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# THE POSTPRANDIAL BLOOD GLUCOSE CONCENTRATION

AS INFLUENCED BY SOME CHANGES IN TYPE AND AMOUNT OF  
CARBOHYDRATE IN THE MEAL AND BY POST MEAL SLOW WALKING

by

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*“The time to translate evidence into practice for diabetes is NOW”*  
*International Diabetes Federation (IDF), Call to action on Diabetes, 2010*

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*Series of dissertations submitted to the  
Faculty of Medicine, University of Oslo  
No. 1347*

ISBN 978-82-8264-451-8

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## ACKNOWLEDGEMENTS

This work was carried out at the Institute of Health and Society from 2008 to 2011. The project was supported by grants from Idun Industrier AS.

Several people have contributed to this project and I would like to thank you all for your support and inspiration.

First of all I would like to thank my principal supervisor, Professor Arne T. Høstmark, from the bottom of my heart. Thank you so much for suggesting the studies and for an outstanding supervision through it all. You have always been there for me, given me rapid feedback on my work and a continuous flow of brilliant suggestions and good advice. I would also thank you for sharing so generously of your knowledge and new ideas and for letting me take part in your very innovative projects. It has been a huge privilege to have you as my supervisor. You have been the best tutor I could ever have wished for and a tremendous source of inspiration. I could never have achieved this without you.

Further, I would like to thank my co-supervisor Professor Gerd Holmboe–Ottesen for valuable support during this period. As the academic head of the department, your involvement in the initiating process with Idun was very important. Thank you so much for all your valuable inputs all the way.

It has been a great pleasure to work with Idun Industrier and Trond Olsen. I think highly of your professionalism, your eagerness to develop beneficial products and your interest in diabetes prevention. Your enthusiasm and positive outlook has been very catching. Thank you also to Jone Voll for making this possible and to Rasmus Selseth, Brit Bjørkli and Trond Wenner and all the other people I have met at Idun. It has been a great pleasure to work with all of you.

I would like to acknowledge the very important contribution from Eva Kristensen who on a daily basis has helped me with many practical issues. Your vast experience and knowledge have been very important. You have probably been my closest mentor. Thank you all the fun we have had as well.

Thank you to Monica Morris for organizing the volunteers for the trials. You were instrumental in finding the volunteers and being present during the experiments.

A warm thank goes to everyone who has participated in the experiments.

My heartfelt thanks goes to my dearest friend Victoria Telle Hjøllset for giving me a kick start by introducing me to “your” supervisor, Professor Høstmark, and “your” project. Thank you so much for sharing so generously from all your experience and wisdom both on a professional and a personal level. Your go-ahead spirit has helped me a lot. It has been a great advantage to have a close friend who is also a colleague. We share a lot and we go back a long way. In that way work has become pleasure. Your friendship has been second to none. I

would never have done this without you. Thank you also to Benedikte Bjørge for welcoming me into the InnvaDiab-DEPLAN project.

Thanks to all my colleagues in the department of Health and Society and to my fellow PhD students for fruitful discussions and for creating a scientific atmosphere around me. A special gratitude is due to Professor Akhtar Hussain and Professor Bjørgulf Claussen for frequent advice, for letting me take part in your “Diabetes network” and for making all the interesting diabetes lunches a reality.

To Ida Bay and Julia Mbalilaki, thank you for playing a key role in creating an inspiring environment in our facilities in Gydas vei. A great thank to Ida for doing all the lipid analysis though outside this thesis.

Thank you to my dear parents and my dear sister Cecilie for continuous support and encouragement throughout my life. Thank you also very much for all the practical support with the children. This has meant a lot to all of us.

Thanks to my dearest children, Halvor, Fredrik and Maria for never letting me forget what is important in life and for being so enthusiastic on behalf of “mamma”. Last of all thank you to my long suffering husband, Kjell Tomas. Thank you for your critical support and for being there for me. I love you.

This has been a very inspiring period of my life. It has been a great pleasure for me to work with everyone involved in this project. I hope our roads will cross again in the future. Thank you so much.

Marianne Sylvana Haug Lunde

Oslo, 06.01.2012

# ABSTRACT

## Background

The burden of obesity, type 2 diabetes (T2D) and cardio-vascular diseases (CVD) is rapidly increasing worldwide. Impaired glucose tolerance (IGT), in which the blood glucose level is higher than normal but not as high as in diabetes, is also a major public health problem. People with IGT have a higher risk of developing T2D and CVD, and especially the magnitude and duration of the postprandial blood glucose concentration (PPG) seems of crucial importance.

In Norway, immigrants from Pakistan have a high prevalence of T2D, especially women. The International Diabetes Federation (IDF) suggests that reducing PPG is important for achieving HbA<sub>1c</sub> goals, probably even more important than control of the fasting level. IDF further states that there is a progressive relationship between plasma glucose levels and CVD risk well below the diabetic threshold. Thus, reducing the post meal glucose levels could be important for T2D/CVD prevention.

Therefore, it seemed of interest to study to what extent moderate meal changes would influence PPG in a group of diabetes prone female Pakistani immigrants. Since previous studies in healthy ethnic Norwegians had shown a PPG-blunting effect of light post meal physical activity, we wondered if the very low intensity activity (slow walking) usually practised by these women, would have a similar effect.

## Aim

The main aim of this thesis was to investigate the extent to which moderate variations in the amount and type of carbohydrates in a meal, and post meal slow walking, might acutely modify the PPG in female Pakistani immigrants living in Oslo, Norway.

## Method

Applying a cross-over design, 31 female Pakistani immigrants living in Oslo were recruited from participants of the completed InnvaDiab Study to participate in experiments where their blood glucose concentration was measured every 15 min for 2h after intake of various amounts and types of a carbohydrate food, either while resting after the meal or doing very light post meal walking of two durations. The carbohydrate rich meals included three different

types of bread (regular bread, and pea fibre enriched bread with two levels of rapeseed oil), cornflakes with milk, and chick peas with onion and tomato.

## Results

Intake of an amount of pea fibre enriched bread containing 25 g CHO attenuated the postprandial peak glucose value (PV,  $p<0.05$ ), the Incremental Area Under the glucose vs. time Curve (IAUC,  $p<0.05$ ) during 15 to 75 min, the glycaemic profile (GP,  $p<0.05$ ), and increased the duration of satiety ( $p<0.05$ ), as compared with intake of regular bread with 25 g CHO. There was no difference between fibre enriched bread with or without rapeseed oil in PV, Incremental peak value (IPV) or IAUC.

Satiety ratings after intake of 25 g CHO in regular coarse bread was 7-23 % lower than corresponding ratings after intake of 25 g CHO in the fibre enriched breads at all observation time points from 60 to 120 min ( $p < 0.05$  for all time points).

A sustained elevated PPG was found after intake of cornflakes providing 75g available CHO. When reducing the cornflake intake to obtain 25g CHO we found reductions in PV of 11% ( $p=0.008$ ) and IAUC of 51% ( $p=0.003$ ). IAUC was reduced by 40% ( $p=0.001$ ) in response to halving the amount of bread.

PPG was also appreciably lowered after intake of 50g CHO given as cooked chick peas spiced with tomato and onion, compared to the same amount of available CHO as corn flakes with milk. Change to chick pea type of CHO resulted in a 15.7% reduction in PV ( $p=0.0001$ ), and 50.9% reduction in IAUC ( $p=0.0001$ ), and increased the time to reach PV (TTP), on average by 20 min ( $p=0.006$ ), and the glycaemic profile (GP) by 73.5% ( $p=0.002$ ). The order of post meal blood PV to one CHO type (amount) corresponded well with the response order to another CHO type (amount) ( $r>0.9$ ,  $p<0.001$ ).

When resting after intake of 50g CHO, the blood glucose concentration increased during the first 30 to 45 min, reaching a maximum value of 9.1 mmol/L after 45 min. Then the glucose concentration decreased but was still about one mmol/L higher than at baseline at the end of the experiment, i.e. at 2h. When 20 min very slow post meal walking was performed after intake of the same meal the mean PV was lowered by 8.2% (NS), and time to reach the PV was delayed, on average by 19 min ( $p=0.002$ ). These effects of walking were strengthened

when the postprandial walk was increased to 40 min. In this latter experiment the time to reach PV from zero time (TTP) was delayed by 25 min ( $p=0.001$ ) and the PV was lowered by 16.3% ( $p=0.001$ ). Additionally, after postprandial walking, the blood glucose concentration approached baseline levels after 2h.

A significant reduction ( $p<0.05$ ) in systolic blood pressure (SBP), but not diastolic blood pressure, was observed in response to 40 min postprandial walking as compared with resting after the meal.

### **Conclusion**

In diabetes prone subjects the PPG can be appreciably blunted both by reducing the quantity and changing the quality of the ingested carbohydrates, and by light post meal walking. The study suggests that there are “high- and low responders” to a carbohydrate load, below the blood glucose threshold indicating diabetes.



## LIST OF PAPERS

### Paper I:

Lunde MSH, Hjellset VT, Holmboe-Ottesen G, Høstmark AT;

#### **Variations in postprandial blood glucose responses and satiety after intake of three types of bread**

*Journal of Nutrition and Metabolism*, vol. 2011, Article ID 437587, 7 pages, 2011.

doi:10.1155/2011/437587

### Paper II:

Lunde MSH, Hjellset VT, Høstmark AT;

#### **Adjusting the amount and type of carbohydrate in a meal strongly reduced the post meal glycemic response in Pakistani immigrant women**

*Journal of Diabetology*. Revised article is under consideration (Nov. 2011).

### Paper III:

Lunde MSH, Hjellset VT, Høstmark AT;

#### **Slow postmeal walking reduces the blood glucose response– an exploratory study in female Pakistani immigrants**

*Journal of Immigrant and Minority health*. Second revision is under consideration (Nov 2011). From the editor (after 1<sup>st</sup> revision): “accepted for publication, conditional on revision in accordance with the suggestions of the reviewers“.

## CONTENTS

Acknowledgements .....	2
Abstract .....	4
List of papers.....	7
Abbreviations and definitions .....	10
Introduction.....	11
Overview in brief .....	11
Physiological significance of blood glucose .....	12
Regulation of the blood glucose concentration .....	13
Some central hormones .....	13
Stress .....	14
Dietary factors.....	15
Physical activity .....	16
Burden of diabetes, globally and in Norway .....	17
Hyperglycaemia .....	19
Effects of hyperglycemia .....	20
Glycation and oxidation .....	24
Approaches to combat high blood glucose levels .....	24
Lifestyle interventions.....	24
Pharmaceutical treatment .....	25
The postprandial challenge.....	25
Regulation of postprandial blood glucose .....	27
Diet.....	27
Physical activity .....	28
Aims.....	29
Research questions .....	29
Methods.....	30
Recruitment.....	30
Design and experimental setup .....	31
Meal experiments .....	33
Light post meal walking.....	34
Order of experiments.....	35
Measurements .....	35
Blood glucose.....	35
Blood pressure.....	36

Satiety .....	36
Anthropometric and blood measurement data.....	36
Statistical analyses .....	36
Ethics.....	37
Main results – summary of papers .....	38
Paper I .....	38
Paper II.....	39
Paper III .....	40
Discussion .....	42
Methodological considerations .....	42
Discussion of main results .....	45
Some additional considerations.....	51
Suggested clinical relevance .....	51
Further research.....	52
Suggested implications for policymakers.....	52
Conclusion: .....	53
Reference list.....	55

## ABBREVIATIONS AND DEFINITIONS

<b>AGE</b>	Advanced glycated end products
<b>CHO</b>	Carbohydrates available for human metabolism
<b>CVD</b>	Cardio-vascular disease
<b>FFA</b>	Free fatty acid
<b>GI</b>	Glycemic index
<b>GL</b>	Glycemic load
<b>GP</b>	Glycemic profile, i.e. the duration of the incremental postprandial blood glucose response divided by the blood glucose incremental peak
<b>HbA<sub>1c</sub></b>	Glycated haemoglobin
<b>HDL</b>	High density lipoproteins/HDL cholesterol concentration
<b>IAUC</b>	The Incremental Area Under the glucose vs. time Curve, calculated by the linear trapezoidal rule.
<b>IDF</b>	International Diabetes Federation
<b>IFG</b>	Impaired fasting glucose
<b>IGT</b>	Impaired glucose tolerance
<b>IPV</b>	Incremental Peak Value (PV), i.e. PV minus the fasting blood glucose concentration
<b>LDL</b>	Low density lipoproteins
<b>LPL</b>	Lipoprotein lipase
<b>MetS</b>	Metabolic syndrome
<b>OGTT</b>	Oral glucose tolerance test
<b>PPG</b>	Postprandial blood glucose concentration
<b>PV</b>	Postprandial blood glucose peak value
<b>T2D</b>	Type 2 diabetes
<b>TG</b>	Triglycerides
<b>TTP</b>	Time to reach PV from zero time
<b>VLDL</b>	Very Low Density Lipoproteins

# INTRODUCTION

## OVERVIEW IN BRIEF

We are facing a worldwide epidemic of diabetes and other non-communicable diseases that share the same risk factors. Increased physical activity, adherence to a healthy diet, smoking cessation and reduction in alcohol consumption remain the cornerstones of lifestyle advices. However, despite having this knowledge, lifestyle diseases seem to increase at an alarming rate, and there is an urgent need to identify lifestyle changes that can be implemented, especially in high risk groups.

Elevated blood glucose concentration, in the fasted state and after meals, is the major characteristic of diabetes. Mal-regulation of the postprandial blood glucose concentration (PPG) is considered as one important risk factor for type 2 diabetes (T2D) and cardiovascular diseases (CVD), and the therapeutic potential of proper regulation of PPG has been extensively documented [1].

*The present work deals with PPG, as acutely influenced by some changes in the type and amount of carbohydrate in the meal, and by post meal light physical activity.*

Control of blood glucose excursions should be especially important in diabetes prone subjects. In Norway, Pakistani immigrants, especially females, represent a high risk group for developing obesity, the metabolic syndrome and T2D [2-4]. Prevention of lifestyle diseases among immigrants has been given considerable attention in Norway during the last decades [5]. The present experiments were carried out in female Pakistani immigrants living in Oslo, i.e. in a group with poor blood glucose regulation.

Although it is well known that the amount and type of ingested carbohydrates may alter PPG, the magnitude of their effects in diabetes prone Pakistani immigrant women seems to be poorly investigated. Furthermore, although previous studies in healthy ethnic Norwegians had shown a blunting effect of light post meal walking on PPG[6], it is not known whether the very low intensity activity (slow walking) usually practised by these women, would have a similar effect. The present work is an attempt to elucidate these questions.

We also used the PPG outcome to evaluate if there are “high- and low responders” to a glucose load. Finally, we examined whether post meal walks might influence the blood

pressure, and whether levels of satiety might differ after intake of different types of bread. The results seemed to give a “yes” to these questions.

We suggest that the present observations might offer a basis for practical lifestyle advice to reduce PPG. Hopefully, if implemented on a population basis, the suggested lifestyle changes should in the course of time imply reduced incidence of T2D and CVD, but we have no data in the present work to substantiate this suggestion.

## PHYSIOLOGICAL SIGNIFICANCE OF BLOOD GLUCOSE

All body tissues are able to utilize plasma glucose for energy production, and for some tissues glucose is the only energy substrate utilizable. In order to function properly the central nervous system requires a constant supply of glucose. Consequently, low blood glucose can lead to symptoms such as lack of concentration or mental confusion, and sustained *hypoglycemia* can lead to brain damage, coma and death. Whereas most tissues can readily utilize free fatty acids or other substrates when glucose becomes unavailable, nerve tissue as well as red blood cells, retina, cells of the intestinal mucosa, renal medulla and gonads epithelium all depend on a continuous supply of glucose. However, during prolonged fasting, the brain starts using ketone bodies as an alternative source of energy.

Abnormal elevation of plasma glucose levels, *hyperglycemia*, does not pose an analogous acute threat, yet prolonged hyperglycemia may also have serious consequences. Severe hyperglycemia sustained for days may lead to glycosuria and dehydration due to osmotic diuresis and decrease in blood volume, reduction of blood pressure, and ultimately coma.

These effects of extreme departures from normal blood glucose levels illustrate the importance of glucose homeostasis, but even relatively small deviations from normal for prolonged periods may have deleterious effects. Conceivably, even modest hyperglycemia over a period of years may account for dysfunction of the nervous system, blood vessels, kidneys, and other tissues.

## REGULATION OF THE BLOOD GLUCOSE CONCENTRATION

### SOME CENTRAL HORMONES

The two hormones that are the most influential in regulating cellular fuel metabolism and blood glucose levels are insulin and glucagon. Depending on whether the body is in a postabsorptive state with energy abundance, or a postabsorptive state where mobilization of endogenous energy is required, these two hormones operate in an antagonistic fashion to regulate the blood glucose concentration. Moreover, several other counter regulatory hormones may also influence blood glucose homeostasis such as adrenalin, cortisol and growth hormone.

### INSULIN

Insulin is a major regulator of the blood glucose concentration. Insulin is an anabolic peptide hormone released from pancreatic  $\beta$ -cells primarily in response to high levels of glucose in the blood. However, insulin secretion rates are also affected by several other factors such as the amino acid concentration in the blood, hormones (incretins), and neural input to the islets of Langerhans.

Insulin facilitates glucose entry into adipose tissues, muscles and liver and is thus lowering the blood glucose levels. In most cells this action is accomplished by mobilization of glucose transporters that translocate from intracellular membranous vesicles to the cell membrane when insulin binds to its receptor [7]. When the insulin signal is withdrawn, the transporter proteins return to their intracellular pool. There are many different types of glucose transporters, but they all work by eliciting facilitated diffusion of glucose across the plasma membrane. GLUT-4 is a glucose transporter that is abundant in tissues such as muscle and adipose which account for the majority of glucose uptake from blood.

The insulin concentration largely governs the carbohydrate-, protein- and fat metabolism [8]. Insulin executes its effects by altering the activities or concentrations of many intracellular enzymes involved in the metabolic pathways of monosaccharides, amino acids and fatty acids in muscle, adipose tissue and liver. High insulin levels promote net storage of carbohydrates, fat and protein, acting by stimulating anabolic processes, and inhibiting catabolic pathways. One example is stimulation of fatty acid synthesis and storage, and inhibition of lipolysis. It has been suggested that chronic hyperinsulinemia may have harmful effects [9].

## GLUCAGON

Glucagon is a peptide hormone released from pancreatic  $\alpha$ -cells in response to low levels of blood glucose. In hypoglycemic states, glucagon acts to increase endogenous glucose supply to blood by stimulating hepatic glycogenolysis, and hepatic *de novo* production of glucose from substrates including lactate, amino acids, and glycerol (gluconeogenesis). The major physiological effects of glucagon occur within the liver and are antagonistic to those of insulin.

Exercise stimulates glucagon secretion even in the absence of changes in blood glucose levels. Contrary to this, high levels of blood glucose and high insulin levels suppress glucagon secretion [8].

## STRESS

In various stress conditions there will be activation of the adrenergic system resulting in release of adrenalin from the adrenal medulla. Adrenalin acts on adrenergic receptors found in the plasma membrane of several tissues.

Adrenalin is important for increasing blood glucose during periods of stress when the sympathetic nervous system is excited. The blood glucose elevating effect of the hormone acts by stimulating breakdown of liver glycogen. Unlike glucagon, adrenalin also stimulates muscle glycogenolysis, but impairs blood glucose extraction by skeletal muscle, so as to further promote elevation of the blood glucose concentration. In addition, adrenalin simultaneously elevates the concentration of fatty acids by activating the hormone sensitive lipase in adipose tissue.

Adrenalin may also influence the output of pancreatic hormones. Thus, in situations of strenuous exercise, elevated adrenaline levels act on adrenergic  $\beta$ -receptors in the pancreas to increase the secretion of glucagon, and at the same time stimulate  $\alpha$ -adrenergic receptors to suppress insulin secretion, thereby reinforcing the mobilization of fuel stores.

Within the Hypothalamic Pituitary Adrenal-system, adrenocorticotrophic hormone (ACTH) is released in response to stress. The synthesis and secretion of cortisol are regulated by ACTH from the anterior pituitary. Cortisol has metabolic effects on a number of tissues to mobilize energy. The hormone increases the blood glucose concentration. In addition, cortisol stimulates the breakdown of fats and proteins, thereby increasing the levels of fatty acids and amino acids in the blood. The mechanisms involve cellular receptors and transcription of genes.



When the stress response is sustained, somatic pathology may develop. Relevant for the risk of the Metabolic Syndrome (MetS) is the sustained stress activation, which may increase the blood glucose concentration through stimulation of hepatic glycogenolysis. It seems that even slight fluctuations in blood sugar may harm endothelial cells. Stress activation may also enhance adipose tissue lipolysis, so as to increase plasma free fatty acids. In the course of time sustained stress may increase the serum triglyceride concentration, and decrease that of HDL. Conceivably, therefore, stress activation may be associated with MetS.

#### DIETARY FACTORS

In the absorptive phase, after a meal, ingested carbohydrates are converted into monosaccharides in the small intestines before they are absorbed into the blood, and glucose is the principal monosaccharide appearing in the circulation. In contrast, other energy containing nutrients do not influence the blood glucose concentration directly. However, meal composition and size may indirectly influence the postprandial blood glucose concentration. Indeed, co-ingestion of fat or protein with carbohydrates has previously been reported to favourably reduce PPG [10,11]. On the other hand, different types of dietary fat and other dietary factors may contribute differently to progression of insulin resistance, as briefly discussed below.

Complex dietary carbohydrates are exposed to amylases even in the mouth, but more extensively so after entering the small intestines where they are acted upon by amylases secreted from the exocrine portion of the pancreas, so as to obtain oligosaccharides and disaccharides. Oligosaccharides and disaccharides require further digestion and breakdown into monosaccharides by the  $\alpha$ -glucosidases present in the brush border of the gut epithelial cells before they can be absorbed. Monosaccharides are absorbed by specific carrier mediated transport processes in the membrane of the intestinal epithelial cells and released into the circulation. However, not all complex carbohydrates are subject to enzymatic breakdown in the small intestine. Any remaining undigested carbohydrates might move into the large bowel where bacteria can metabolize them into short-chain fatty acids (e.g. acetate, butyrate and propionate), and other products, including gases such as methane and hydrogen. Delayed carbohydrate absorption mitigates the postprandial rise in blood glucose.

Carbohydrates in human nutrition can be classified according to the chemical structure, availability/nutritional values, or physiological responses to intake. Already in 1929, McCance and Lawrence realised that not all carbohydrates could be utilized and metabolized

by humans, and hence they categorised dietary carbohydrates into available and unavailable carbohydrates [12]. However, some unavailable carbohydrates may still provide energy through fermentation in the large bowel. A more appropriate way to categorise carbohydrates could be according to their ability to provide carbohydrates that may increase the blood glucose concentration, i.e. as glycemic or non-glycemic carbohydrates. The term available/unavailable is however commonly used and will be used in this thesis, meaning carbohydrates that may or may not be used for metabolism. Dietary fibre are highly complex substances that are non-digestible in the upper gut and do not provide carbohydrates for metabolism [13]. Dietary fibre are classified according to their solubility in water even though categorizing according to viscosity, gel-forming capabilities or fermentation rate by the gut bacteria might be physiologically more relevant. It is well accepted that viscous and gel-forming properties of dietary fibre may inhibit macronutrient absorption, reduce postprandial glucose responses and beneficially influence certain blood lipids [14].

#### PHYSICAL ACTIVITY

During exercise, the glucose expenditure in the muscle cells increases, which in turns increases the glucose clearance from the blood and reduces blood glucose levels. Physical activity increases both the insulin sensitivity and the insulin independent glucose entry into skeletal muscle [15,16], and these mechanisms may be sustained upon exercise cessation. It has been shown that an acute bout of submaximal exercise can lower the blood glucose concentration for 2 to 48h post exercise, and improve insulin sensitivity as long as 72h after cessation of any given exercise bout [17-19].

In response to high intensity physical activity, there is an increase in serum adrenalin concentration. As mentioned in relation to stress activation, this hormone stimulates release of glucose from liver glycogen, and fatty acids from adipose tissue into the blood stream. The working muscle will metabolize these substrates for energy during exercise. However, increased levels of blood glucose and fatty acids may be seen after cessation of physical activity. In healthy subjects these increased levels of glucose and fatty acids may be rapidly corrected by glucose stimulated insulin release. In contrast, subjects with impaired glucose tolerance may experience an augmented duration of high levels of glucose and fatty acids [20]. In particular, the post exercise increase in the fatty acid concentration may be attenuated if the subjects accomplish active recovery, e.g doing low intensity bicycling instead of abruptly discontinuing strenuous exercise [21].

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Maintenance of euglycemia is a critical homeostatic function, since both hypo- and hyperglycemia might have serious negative health effects. In a normal healthy individual this precise system controls fluctuations in blood glucose in a consistent manner. Deviations, such as an increased blood glucose concentration after a meal, are quickly brought back to normal levels through homeostatic control. However, for several decades, urbanization and globalization processes have resulted in rapid changes in eating habits and other lifestyle characteristics such as reduced physical activity and increased emotional stress, and thus challenge the homeostatic mechanisms. This may have contributed to the global epidemic of diabetes and may also play an important role in progression of cardiovascular diseases, both of which representing major challenges for health and development in the twenty-first century [22].

One particular dietary alteration in many countries during the later years seems to be an extensive use of ‘refined’ carbohydrates, often ingested in high amounts by people who also have a sedentary lifestyle. This alteration raises the question of how the post meal blood glucose concentration may respond to acute variations in carbohydrate intake. One aspect of the present work was to elucidate this question.

## BURDEN OF DIABETES, GLOBALLY AND IN NORWAY

The diagnosis of diabetes, its treatment and complications are closely related to the regulation of blood glucose. Diabetes is recognized as a group of heterogeneous disorders with the common elements of hyperglycemias and glucose intolerance, due to insulin deficiency, impaired effectiveness of insulin action (insulin resistance) or both. Diabetes mellitus is classified on the basis of aetiology and the underlying causes of the hyperglycaemia into type 1 diabetes, type 2 diabetes, gestational diabetes and other specific types [23,24]. Type 1 diabetes is generally caused by immune-mediated beta cell destruction with subsequent loss of insulin production. Type 2 diabetes is caused by insulin resistance in combination with relative loss of insulin production [24].

The diagnosis is based on measurement of the fasting blood glucose concentration and the blood glucose level 2h after an oral glucose tolerance test (OGTT) [24]. In a recently

published position statement by the American Diabetes Association, HbA1c was recommended as an alternative diagnostic criteria for the diagnosis of diabetes [25].

Today, 366 million people live with diabetes worldwide, representing 8.3% of the global adult population[26]. While Africa has faced the largest percentage increase over 20 years, the Middle East now has the highest prevalence rates. However, China and India have the highest absolute number of individuals suffering from diabetes [23].

Based on the prevalence of diabetes in several population surveys, the number of people with diabetes in Norway was estimated to be less than 120 000 in 2004, probably with a similar number of undiagnosed subjects [27]. In 2011, the number of diabetic patients in Norway is estimated to be 350 000 [28]. Ethnic minorities living in developed countries usually exhibit a greater risk of developing T2D. They acquire diabetes at an earlier age, accompanied by higher morbidity and mortality rates [29,30]. In Norway, especially immigrants from Pakistan, constituting one of the largest immigrant groups in Norway, have a high prevalence of T2D [2-4]. In fact, for women, impaired glucose tolerance (IGT) was found in 37%, MetS in 41%, and T2D in 12%, using fasting glucose [3].

The rising prevalence of T2D is associated with ageing population, high rates of obesity, dietary changes caused by increased urbanization and migration, sedentary lifestyles and stress[24]. This thesis will focus on post meal blood glucose concentration in subjects prone to T2D. T2D constitutes about 85% to 95% of all diabetes in high-income countries [23].

### *Insulin Resistance*

Insulin resistance may be the first step in the development of T2D. Insulin resistance may be defined as a reduced biological response to a given concentration of insulin. Consequently, insulin stimulated peripheral uptake of glucose in skeletal muscle is reduced and the endogenous glucose production in the liver is increased. It is well known that insulin resistance commonly coexists with obesity. However, causal links between insulin resistance, obesity, and dietary factors are complex and controversial. It is possible that one of them arises first, and tends to cause the other; or that insulin resistance and excess body weight might arise independently as a consequence of a third factor, but end up reinforcing each other. Several dietary factors that may be implicated in the development of insulin resistance

are discussed below. Whatever the cause, insulin resistance is associated with dyslipidaemia, hyperinsulinemia and hyperglycaemia [8].

## HYPERGLYCAEMIA

In people with normal glucose tolerance, plasma glucose generally rises no higher than 7.8 mmol/L in response to meals, and typically returns to pre meal levels within two to three hours [31,32]. The development of T2D is characterized by a progressive decline in the insulin action (sensitivity), and a continued decline in the  $\beta$ -cell function, implying impaired insulin secretion [8]. Prior to clinical diabetes, these metabolic abnormalities are first evident as disturbances in the postprandial glucose concentration, due to loss of the first phase insulin secretion, and decreased insulin sensitivity in peripheral tissues. In addition, also deficiencies in glucoregulatory peptides (amylin)[33,34] and incretin hormones, secreted by the gut, may influence blood glucose levels [35].

Impaired Fasting Glucose (IFG) and Impaired Glucose Tolerance (IGT) refers to a metabolic state intermediate between normal glucose homeostasis and T2D [24]. Both are also known as prediabetes.

The diagnostic criteria for diabetes and intermediate hyperglycaemia have changed during last decade. Current guideline [24] define glucose tolerance according to the table below:

	<b>Fasting value</b> <b>mmol/L</b>	<b>2h post glucose load</b> <b>mmol/L</b>
<b>Impaired Fasting Glucose (IFG)</b>	> 6.1 and $\leq$ 6.9 mmol/L	
<b>Impaired Glucose Tolerance (IGT)</b>	< 7.0 mmol/L	$\geq$ 7.8 and < 11.1 mmol/L
<b>Diabetes (T2D)</b>	$\geq$ 7.0 mmol/L	$\geq$ 11.1 mmol/L

Measured in capillary blood and, for the 2h limit, after ingesting 75g glucose in an oral glucose tolerance test (OGTT).

The American Diabetes Association (ADA) recently recommended lowering the threshold for Impaired Fasting Glucose (IFG) from 6.1mmol/l to 5.6 mmol/l, and also included a HbA<sub>1c</sub> requirement for increased risk of diabetes, 5.7 to 6.4% [36].

Post meal hyperglycemia is defined as a plasma glucose level  $> 7.8$  mmol/L [1]. Elevated or prolonged postprandial glucose elevation is an early sign of diabetes. Glycaemia and diabetes are rising globally, driven both by population growth and ageing and by increasing age-specific prevalence [37].

#### EFFECTS OF HYPERGLYCEMIA

A chronic high blood glucose concentration (hyperglycemia) is both a characteristic and a precursor of type 2 diabetes [38]. Hyperglycemia is also associated with an increased risk of cardiovascular disease and premature mortality, and this association persists below the categorical cut offs for diabetes and impaired glucose tolerance [39,40]. Some effects of hyperglycemia is shown in figure 1. Only some of the links will be mentioned below.

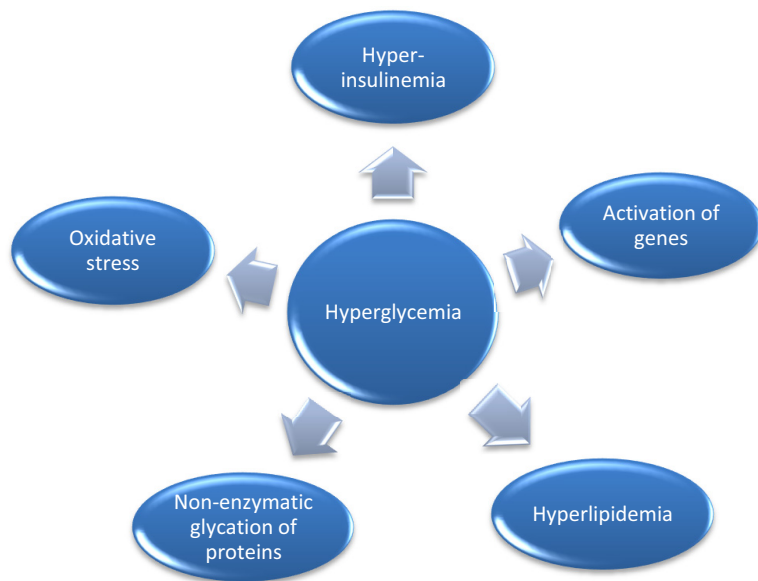


Figure 1. Indication of some effects of hyperglycemia.

*Blood lipids as influenced by dietary fat and carbohydrates.*

Both dietary fat and carbohydrate can influence plasma low density lipoprotein (LDL). In brief, dietary fat appears in the circulation as chylomicrons, formed in the intestinal cells. As the chylomicrons pass through the capillaries of various tissues, such as adipose tissue, skeletal muscle and heart, triglycerides are hydrolyzed by lipoprotein lipase (LPL) in the capillary wall. The fatty acids released from the chylomicron triglycerides enter the cells where they e.g. can be used for energy production, or be esterified and stored as triglycerides. Some of the released fatty acids may bind to serum albumin, eventually to be utilised by various tissues. Chylomicron remnant particles are rapidly cleared from the plasma by binding to the hepatic Apo E receptors, followed by endocytosis. Inside the liver, the remnants may be further broken down, and the fatty acids may be used for energy production, or esterified to triglycerides and used for synthesis of VLDL particles, which in the plasma compartment are converted to LDL. In this way dietary fat can appear as LDL in plasma.

However, also dietary carbohydrate can be metabolized to esterified fatty acids in plasma LDL. A crucial intermediate in the synthesis of triglycerides from carbohydrates is acetyl coenzyme A, which is the key substrate for *de novo* synthesis of fatty acids. When the synthesised fatty acid chains have grown to contain 14 to 18 carbon atoms they combine with glycerol to form triglycerides, a major component of VLDL. After exocytosis, VLDL is converted to LDL in the bloodstream.

Sucrose is a major carbohydrate source in Norway. This disaccharide consists of glucose and fructose. The formation of acetyl coenzyme A from glucose is controlled by an extensive regulation of the phosphofructokinase step, and also by feedback inhibition of hexokinase by glucose-6-phosphate. In contrast, by circumventing these regulatory steps, fructose is rapidly converted to acetyl CoA. Therefore, fructose may have a stronger lipogenic effect than glucose and starches. Indeed, repeated intake of fructose, but not of glucose, resulted in an acute increase in the serum triglyceride concentration in young men [41]. Since carbohydrate derived fatty acids will be of the saturated type, whereas those formed from chylomicron will reflect dietary fat, VLDL and LDL derived from dietary fat might be more unsaturated than lipoproteins derived from carbohydrates, provided that unsaturated oils are used in the diet.

Dietary fat has long been implicated as a driver of insulin resistance. One line of reasoning is that during LPL catalyzed chylomicron lipolysis following a fat meal, some of the released fatty acids will be taken up by serum albumin and transported to various tissues. Elevation of

the plasma fatty acid concentration may in turn enhance intracellular fat accumulation [42]. For skeletal muscle, increased intracellular lipid content may induce insulin resistance [43]. However, in this context it seems pertinent to raise the question of whether also high intakes of carbohydrate, especially of fructose, may cause increased VLDL and LDL production, and also increased levels of serum fatty acids [44]. During VLDL catabolism, FFA will be released, bound to serum albumin and taken up by peripheral cells. Additionally, LDL will be taken up in cells via the apo B receptors, thereby giving increased cellular lipids. Therefore, also excess carbohydrate intake may contribute to insulin resistance through the same mechanisms as dietary fat. In contrast, n-3 fatty acids has been shown to strongly reduce insulin resistance and improve glucose tolerance in animal models [45]. However, data from human and animal studies are inconsistent [46].

Insulin resistance may possibly also be due to simultaneous high supply of fatty acids and glucose for oxidation in muscle tissue, as could be the case in prediabetes. The interaction between glucose and fatty acid metabolism was first described by Randle and colleagues in 1963 [47] and again clarified with evidence in man *in vivo* by Randle in 1998 [48]. A major point in this interaction is a mechanism whereby the oxidation of fatty acids in the muscle reduces uptake and oxidation of glucose, with a net result of high blood glucose levels in the circulation. A number of *in vitro* studies have shown that fatty acids can induce  $\beta$ -cell apoptosis in the presence of high glucose and that unsaturated fatty acids are protective [49].

Since substituting iso-energetic amounts of fat with carbohydrates has been found to increase plasma triglyceride levels and lower HDL-cholesterol levels in some controlled studies, there has been a discussion as to whether high carbohydrate/low fat diets are the most suitable diets for people with type 2 diabetes [50-52]. Further, exogenous insulin is known to promote weight gain, and slow weight loss. Opponents of the low fat/high carbohydrate diet, advocated by most dietary recommendations for the last decades, have suggested that a diet lower in carbohydrate and higher in fat and protein might be beneficial for weight reduction in insulin resistant subjects, due to lower insulin requirements on this type of dietary regimen [53-55].

#### *Dietary recommendations*

The clinical use of low carbohydrate diets is still debated due to lack of long term data. However, the American Diabetes Association (ADA) changed their dietary recommendations from advocating against the use of low carbohydrate diets [56] to acknowledging such diets as



being as effective as low fat diets in reducing body weight and improving CVD risk factors over a time span up to one year. In addition, the use of low glycemic index foods that are rich in fibre and other important nutrients, were encouraged [57].

In line with the ADA recommendations, there is also consensus in the dietary guidelines for the Asian Indian population to allow for a small reduction in the intake of carbohydrates (to 50-60% of the total calorie intake), preferential intake of complex carbohydrates and low glycemic index foods, higher intake of fibre, lower intake of saturated fats, optimal ratio of essential fatty acids, reduction in trans fatty acids, slightly higher protein intake, lower intake of salt, and restricted intake of sugar [58].

The European Association for the study of Diabetes (EASD) has summarized the evidence for recommended diet in the treatment of type 2 diabetes. The dietary recommendation for the Norwegian general population reflects this guideline [59].

#### *Hyperglycemia and obesity*

In humans, the liver is responsible for the conversion of excess dietary carbohydrates into triglycerides (TG), through *de novo* lipogenesis [8]. The physiological importance of *de novo* lipogenesis in humans has been considered to be of minor importance in healthy subjects [60]. However, the importance of hepatic *de novo* lipogenesis in contribution to hypertriglyceridemia has been difficult to assess due to methodological limitations. More recently, carbohydrate dependent fatty acid formation in the liver has been found to play an important role in the production of triglycerides after intake of high carbohydrate/low fat diets, and in conditions of hyperinsulinemia [61].

Although insulin is a central regulator of the lipogenic pathway, it is now accepted that glucose also generates an independent signal. Glucose is not only an energy source but also controls the expression of key genes involved in energetic metabolism, through the glucose-signaling transcription factor, Carbohydrate Responsive Element Binding Protein (ChREBP). ChREBP has emerged as a central regulator of *de novo* fatty acid synthesis (lipogenesis) in response to glucose under both physiological and pathological conditions [62,63]. These mechanisms may explain weight gain related to excess carbohydrate intake.

## GLYCATION AND OXIDATION

Hyperglycemia *per se* is not desirable, since the glucose molecules will promote glycation of proteins. The glycation process starts as a non enzymatic reaction between glucose and amino acids, to form Schiff-bases that may turn into more stable Amadori-products during the following days. Amadori-products are precursors for Advanced Glycation End products (AGE), which have harmful cellular effects [64,65]. Glycation of proteins may involve proteins found in the circulation, such as lipoproteins, albumin, and other serum proteins, but probably also proteins serving as endothelial receptors. Even intracellular proteins could be glycated [66]. Modification of low-density lipoprotein (LDL) can lead to alteration of the apoB protein to the extent that it is no longer recognized by the regulated cholesterol-feedback receptors. Instead, this modified LDL is taken up via scavenger receptors of subendothelial macrophages, a process which in the course of time might promote atherosclerosis [67].

Numerous studies support the hypothesis of a causal relationship between hyperglycaemia and oxidative stress [68,69]. Oxidative stress plays a pivotal role in the development of diabetes complications, both microvascular and cardiovascular [70].

## APPROACHES TO COMBAT HIGH BLOOD GLUCOSE LEVELS

### LIFESTYLE INTERVENTIONS

Randomized controlled trials have unequivocally demonstrated that lifestyle management is highly efficient in the prevention and early management of T2D [71]. Nutritional intervention, physical activity and weight control remain the cornerstones of prevention of lifestyle diseases. There is a broad consensus about the importance and benefits of regular physical activity and maintenance of desirable body weight. However, there is considerable debate regarding the optimum diet composition.

In the Finnish Diabetes Prevention Study continuing detailed, personalized recommendations about diet and exercise reduced the incidence of new-onset diabetes by 58% compared with the group receiving only general instructions [72]. Diet and exercise in the Malmö study decreased new-onset diabetes by more than 50% compared with the control group [73]. After 12 years, the mortality in the intervention group was not different from that observed in the normal glucose tolerance cohort [74]. The Da Qing trial demonstrated that diet alone, exercise alone, or their combination significantly reduced the incidence of diabetes [75]. In the US

Diabetes Prevention Program study [76], an intensive program of lifestyle modification designed to achieve and maintain at least a 7% loss of body weight through a healthy, low-calorie, low-fat diet combined with an exercise program reduced the incidence of diabetes by 58% compared with the standard lifestyle intervention placebo group.

In 2011 [77] Saito et. al. suggested that 3-year individual-based lifestyle intervention could prevent type 2 diabetes mellitus among overweight Japanese with impaired fasting glucose levels.

#### PHARMACEUTICAL TREATMENT

Pharmaceutical treatment is beyond the scope of this thesis and will only be mentioned briefly. Lifestyle interventions have been shown to be more effective in preventing T2D compared to drug treatment [76,78]. However, drugs are needed when treatment goals are not met with lifestyle interventions alone [79]. At present, the major drugs to treat diabetes mellitus are insulin, insulin analogues, insulin secretagogues such as sulfonylureas or glinides, biguanides and glitazones decreasing the hepatic glucose production and increase glucose utilization in peripheral tissues, as well as  $\alpha$ -glucosidase inhibitors delaying carbohydrate absorption. Although many agents improve overall glycaemic control, including postmeal plasma glucose levels, several pharmacologic therapies specifically targets postmeal plasma glucose [1]. Traditional therapies include  $\alpha$ -glucosidase inhibitors and rapid acting insulin and insulin secretagogues. More recent therapies address deficiencies in pancreatic and gut hormones that affect insulin and glucagon secretion, satiety and gastric emptying, such as glucagon-like peptide-1 (GLP-1), dipeptidyl peptidase-4 (DPP-4) inhibitors and amylin analogues [80].

Like dietary fibres,  $\alpha$ -glucosidase inhibitors delay intestinal absorption of carbohydrates [81].  $\alpha$ -glucosidase inhibitors accomplish their effect by binding competitively to the carbohydrate-binding region of  $\alpha$ -glucosidase enzymes at the intestinal brush border, thereby competing with oligosaccharides and preventing their cleavage into absorbable monosaccharides. The net result is a decrease in the rise in plasma glucose concentration after ingestion of complex carbohydrates [82].

#### THE POSTPRANDIAL CHALLENGE

The postprandial blood glucose concentration is of crucial importance for progression of diabetes and CVD [83,84]. In a meta-analysis of observational studies from 2008, Barclay et

al. [85] found that postprandial hyperglycemia contributes to chronic disease, independently of diabetes status. Benefits of reducing PPG levels have been demonstrated in connection with chronic diseases in general [86,87] and for CVD [84,88], diabetes and obesity [1,87] in particular. The harmful effects of postprandial hyperglycemia may partly be related to the production of free radicals. As shown by Ceriello et al. intake of a carbohydrate meal is followed by oxidative stress that is related to the level of hyperglycemia [89], and also to fluctuations in blood glucose levels [90]. It seems accordingly of special importance to avoid sustained hyperglycaemic episodes and large blood glucose fluctuations during the day. Since the highest glucose levels occur in the postprandial period, one should in particular secure glycemic control in this period, and especially after ingestion of high glycemic foods, for example bread or cornflakes.

There is however, debate about the respective impact of PPG and fasting glucose levels in T2D subjects. Monnier et. al [91] suggested that the relative contribution of PPG to the overall glycaemia is high in diabetes prone subjects with near to normal HbA<sub>1c</sub>.

### *Ethnicity and PPG*

Both genetic and cultural factors might contribute to the disparity in the prevalence of T2D across population groups. Dickinson et al. (2002) found that the postprandial hyperglycemia and insulin sensitivity varied among different ethnic groups, and that lean, young South East Asians had the highest postprandial glycemia and the lowest insulin sensitivity in response to a realistic carbohydrate meal [92]. In line with this, Venn et. al [93], found differences between people of Asian and Caucasian ethnicity in their glycemic responses to a glucose load, and also to a commonly consumed breakfast cereal. Furthermore, female Pakistani immigrants living in Norway show a higher prevalence of T2D than female Pakistani in their native country indicating an additional cultural component [94]. Kandula et al. [95] found a higher prevalence of T2D among acculturated immigrants and concluded that acculturation is a factor that should be considered when predictors of T2D in immigrants are examined. It seems that Pakistani immigrants in Norway adopt the local habits concerning use of carbohydrate rich food items [96]. However, to our knowledge it has not been established to what extent the elevated T2D prevalence found among immigrants in Norway have cultural or genetic explanations.

## REGULATION OF POSTPRANDIAL BLOOD GLUCOSE

### DIET

A number of factors influence glycemic response to food [97], including the amount of carbohydrate [98], type of sugar (glucose, fructose, sucrose, lactose) [99], nature of the starch (amylose, amylopectin, resistant starch) [100], cooking and food processing (degree of starch gelatinization, particle size, cellular form) [101], and food structure [102], as well as other food components (fat and natural substances that slow digestion—lectins, phytates, tannins, and starch-protein and starch-lipid combinations) [103]. Fasting and preprandial glucose concentrations [104], the severity of glucose intolerance [105], and the second meal or lente effect [106,107] are other factors affecting the glycemic response to food.

### TYPE AND AMOUNT OF CARBOHYDRATES

Postprandial blood glucose is largely influenced by the carbohydrate load of the meal implying that diets with low glycemic loads are beneficial in controlling postmeal plasma glucose [108]. The concept of glycemic index (GI) was introduced by Jenkins et al in 1981 [108] to quantify the glycemic effect of carbohydrates in different foods. Conceivably, also the *amount* of carbohydrate ingested influences the glycemic effect. The *glycemic load* (GL) of a portion is defined as the product of GI and amount carbohydrate in the portion [109]. Thus GL of a food portion is a ranking system for the blood glucose impact of ingested carbohydrates. Most of the modern starchy foods, such as breads have relatively high GI, implying high GL after intake of relatively small amounts.

Bread is a major food item in Norway, but is generally high glycemic. However fibre enriched bread may have reduced GI. Thus, among several other health benefits, dietary fibre seems to have a beneficial influence on glucose homeostasis. It is generally recommended that people should be encouraged to increase their fibre consumption, e.g. from whole grains and pulses [110]. However, inclusion of fibre and whole grains seems to complicate the industrial production of bread.

Pea fibre has traditionally not been a common ingredient in bread recipes. It is however known that intake of whole peas will influence blood glucose level [108]. Accordingly, replacing available carbohydrates in breads by pea fibre may potentially reduce the glycemic impact of such breads. In 2009, Marinangeli et.al concluded that whole yellow-pea flour can be used to produce low glycemic functional foods possessing sensory attributes that are

comparable to identical food products containing whole wheat flour [111]. The baking industry in Norway has recently succeeded in making pea fibre enriched bread without compromising the bread production methods. This achievement made it possible to study the effect of a pea fibre enriched bread on PPG in diabetes prone Pakistani immigrant women.

#### PHYSICAL ACTIVITY

Data from observational and randomised trials suggest that approximately 30 minutes of moderate intensity physical activity, such as walking, at least 5 days per week may substantially reduce the risk of developing T2D [112]. In line with this, Norwegian health authorities recommend minimum 30 min of physical activity per day at an intensity of 12-13 on the Borg's scale [113,114].

Physical activity performed immediately after a meal has repeatedly been found to blunt the blood glucose increase after a carbohydrate meal in healthy ethnic Norwegians. Høstmark et. al. showed, in 2006, that the postprandial glucose concentration can be appreciably attenuated by light post meal physical activity, as observed both in healthy young and middle-aged, sedentary and trained women [115]. These findings were subsequently extended to include also lower intensity post meal physical activity, i.e. bicycle exercise at 59 to 67 % of  $HR_{max}$  [6], and post meal walking. Indeed, the magnitude of the blood glucose blunting effect of walking after a meal was comparable to that of the  $\alpha$ -glucosidase inhibitor acarbose [116]. These previous findings raise the question of whether also the very low activity (slow walking) usually practised by these women would have a similar effect.

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The burden of T2D and CVD is large both on the community level and for each and every person who suffers. There is an urgent need worldwide to identify strategies to slow the progression of the current epidemic of these diseases that have proven to be preventable by lifestyle changes. Mal-regulation of postprandial blood glucose values may be one of the most important risk factor for T2D and CVD in diabetes prone subjects. The therapeutic potential of proper regulation of PPG has been extensively documented. Previously, PPG has been shown to be attenuated by dietary modifications and light post meal physical activity in healthy individuals. Since female Pakistani immigrants living in Oslo are a high risk group for developing diabetes, it would of seem crucial importance to further clarify to what extent

dietary modification within the carbohydrate part of a meal, and light post meal physical activity might influence the PPG, without pharmaceutical treatment.

## AIMS

As outlined, disturbances in blood glucose levels are implicated in the development of lifestyle diseases that pose major health challenges in the world today, such as obesity, T2D, and CVD. An adequate regulation of the blood glucose concentration is therefore crucial for the prevention and treatment of these diseases. Since the highest blood glucose levels are encountered after carbohydrate meals, addressing postprandial blood glucose elevations after such meals seems of particular importance to achieve improvements in blood glucose control, especially in diabetes prone subjects. Current lifestyle advice recommends a healthy diet, and an increase in the level of physical activity, but do not specifically relate to the postprandial period. Therefore, it seemed of interest to elucidate to what extent some modifications in amount and type of ingested carbohydrate meals, as well as post meal physical activity, would influence the postprandial blood glucose concentration in diabetes prone subjects.

## RESEARCH QUESTIONS

In a group of diabetes prone subjects, to what extent will

- 1) - the postprandial blood glucose (PPG) response to ingested carbohydrates be influenced by replacing some of the digestible carbohydrates in bread with pea fibre?
- 2) - inclusion of rapeseed oil in the fibre enriched bread influence the PPG response?
- 3) - the satiety be influenced by using pea fibre enriched bread as compared with regular coarse bread?
- 4) - a moderate variation in type and amount of carbohydrates influence PPG?
- 5) - there be variation between subjects in PPG after intake of the same amount of carbohydrates, i.e. high and low responders to ingested glucose, among subjects with normal fasting blood glucose concentration?
- 6) - very slow postmeal walking attenuate the post meal blood glucose response and blood pressure?

## METHODS

### RECRUITMENT

The present studies sought to clarify postprandial blood glucose responses in diabetes prone subjects. Therefore, all participants were recruited from diabetes prone Pakistani immigrant women who had previously participated in the InnvaDiab-DEPLAN project [3]. During the first phase of the InnvaDiab-DEPLAN project it became evident that there was an urgent need to identify lifestyle changes that were effective and easy to implement. 198 Female Pakistani immigrants living in a suburban area of Oslo (Søndre Nordstrand) were included in the complete InnvaDiab study.

After completing the InnvaDiab-DEPLAN, 31 of participants were randomly recruited to participate in cross-over design experiments, to study the postprandial glucose concentration as influenced by amount and type of carbohydrate in the meal, and by post meal walking. Inclusion criteria were: women living in Norway and born in Pakistan or women born in Norway by two Pakistani parents, 25 years or older. Exclusion criteria were: self-reported T2D, glucose lowering pharmaceutical treatment, heart diseases, close relatives already in the project, pregnancy. 20 subjects had been allocated into InnvaDiab-DEPLAN intervention group and 11 subjects had been allocated into the control group of InnvaDiab-DEPLAN.

The Urdu- and Punjabi speaking project coordinator engaged in the InnvaDiab-DEPLAN project was in charge of the recruitment. She contacted InnvaDiab-DEPLAN participants with an invitation to participate in experiments regarding postprandial glucose concentration. The participants were given verbal information in the preferred language about the experiments, and their right to withdraw from the project at any time without a given reason. The project coordinator stayed in touch with the women during the intervention, reminding them of the scheduled sessions, and was present during the sessions for practical assistance during the experiments.

All 31 participants had a waist circumference  $\geq 80$  cm, and 30 (of 31) were overweight or obese according to WHO definition for south East Asians (BMI above  $23 \text{ kg/m}^2$ ). Thus, all participants were considered diabetes prone. Following a standardized OGTT performed in the InnvaDiab-DEPLAN study, 29 of the subjects had normal fasting blood glucose, but only 14 had normal blood glucose values 2h after intake of 75 glucose, Table 1.



**Table 1. Diabetes related blood glucose characteristics of the participants.**

<b>Diagnosis</b>	<b>Fasting Blood glucose</b>	<b>2h blood glucose</b>
Normal glucose tolerance (NGT)	Fasting BG < 6.1 mmol/L <b>n=29</b>	2h BG < 7.8 mmol/L <b>n=14</b>
Impaired fasting glucose (IFG)	Fasting BG ≥ 6.1 mmol/L <b>n=1</b>	
Impaired glucose tolerance (IGT)		2h BG ≥ 7.8 mmol/L <b>n=10</b>
Unknown diabetes	Fasting BG ≥ 7.0 mmol/L <b>n=1</b>	2h BG ≥ 11.1 mmol/L <b>n=7</b>

## DESIGN AND EXPERIMENTAL SETUP

In this project we conducted several experiments to study the acute effect of some lifestyle interventions on the blood glucose concentration. The experimental settings sought to imitate everyday activities by choice of test meals and walking conditions. Great care was taken to bring about a comfortable atmosphere to avoid emotional stress which could have repercussion for the blood glucose concentration.

The 31 subjects were divided into three groups which were given different carbohydrate containing meals, and performed post meal slow walking according to table 2.

**Table 2. Allocation into groups to study modifications of the PPG response.**

<b>Subjects</b>	<b>Intervention</b>	<b>Presented in paper no.</b>
<b>Group A</b> <b>(n=10 )</b>	25 g CHO as high fibre/low fat bread	I
	25 g CHO as high fibre/high fat bread	I
	25 g CHO as low fibre/low fat bread	I and II
	50 g CHO as low fibre/low fat bread	II
<b>Group B</b> <b>(n=10 )</b>	25 g CHO as cornflakes with milk	II
	50 g CHO as cornflakes with milk	II
	75 g CHO as cornflakes with milk	II
	50 g CHO as chick peas, tomato and onion	II
<b>Group C</b> <b>(n= 11)</b>	50 g CHO as cornflakes with milk, resting	III
	50 g CHO as cornflakes with milk, 20 min light post meal walk	III
	50 g CHO as cornflakes with milk, 40 min light post meal walk	III

On separate days and after an overnight fast, the subjects participated in several experiments, in a cross-over design. On experimental days, fasting blood glucose concentration was measured in triplicate i.e. 3 measurements were carried out on 3 consecutive drops of blood, from the same finger prick, and subsequently a test meal was served. The subjects consumed the meal in a comfortable place within 15 min. The post meal blood glucose concentration was measured repeatedly during a 2h period after the start of the test meal. The participants sat resting for the entire 2h period except for the experiments in group C that included a 20 min or a 40 min post meal light walk. The order in which each intervention in a particular group was given was randomly selected by drawing lots. However, all participants attained the same experiment on a particular experimental day.

We anticipated that there might be day-to-day differences between the different days of the week regarding diet and physical activity. Thus, we choose to have one week between subsequent sessions. The participants were asked to behave as similarly as possible on the day before the experiments with regard to physical activity, and to fast for 12 hours before the experiments started in the morning.

The primary outcome of studies of PPG was the overall postprandial glycemia, as estimated by several measures (see Statistical analysis). Secondary outcome depended on intervention and included satiety and blood pressure, respectively.

#### MEAL EXPERIMENTS

The portion sizes of the food given were calculated according to data for macronutrient composition, including available carbohydrate and dietary fibre provided by the manufacturers.

#### *Bread*

Bread is a cornerstone in the Norwegian diet. In fact, in a study from 2008, eight out of ten reported eating bread for breakfast and lunch regularly. Only three percent reported not eating bread at any of the daily meals. A high intake of whole wheat bread is a typical characteristic of Norwegian bread habits [117]. To increase the consumption of whole wheat bread and grain products has been a primary goal set out in the Norwegian Government's plan of action for a better diet in the population for the period of 2007-2011.

Group A subjects were served three types of sliced bread (Idun Industrier, Norway) if preferred toasted, with 2 dl of tap water. The portion sizes of bread were calculated so as to obtain 25 g (all three types of bread) or 50 g (only low fibre /low fat bread) available CHO.

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**Table 3. Contents of bread**

<b>Content</b>	<b>Bread types</b>		
	<b>Bread 1</b>	<b>Bread 2</b>	<b>Bread 3</b>
	<b>(low fibre, low fat)</b>	<b>(high fibre, low fat)</b>	<b>(high fibre, high fat)</b>
	Per 100 g	Per 100 g	Per 100 g
Dietary fibre (g)	4.6	17	17
Available carbohydrate (g)	40.1	21	19
Fat (g)	2.8	1	9

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### *Cornflakes*

Cornflakes is a well known cereal which have previously been used to investigate the effect of post meal physical activity. Cornflakes are made from maize starch that are easily digested and hence hold a high GI value.

Group B was served three different portion sizes of Cornflakes (Kellogs Ltd.; 84.0g available CHO and 3.0g fibre/100g) with semi skimmed milk (Tine Meierier, Norway; 4.7g available CHO/100g). The amount of milk was kept constant at 2 dl per portion but the amount of cornflakes was calculated to obtain 25g, 50g or 75g of available CHO per portion respectively.

### *Chick peas*

After having performed the three cornflake experiments the women suggested another experiment with their own food, letting us know that they understood not only that postprandial glucose levels are influenced by the quantity but also could be influenced by the quality of carbohydrates. We chose chick peas with onion and tomatoes.

Thus, group B was served a meal consisting of canned chick peas (Viter, Spain) (19.6g available CHO and 5.4g fibre/100g) flavoured by some small tomato pieces (3.3g available CHO and 1.3g fibre/100g) and onion pieces (9.1g available CHO and 2.1g fibre/100g) prepared to include 50g available CHO.

### LIGHT POST MEAL WALKING

A practical approach was applied to determine the experimental conditions in the light post meal walking experiments. We anticipated that conditions as near-to-normal as possible would be beneficial for the participants to later translate this knowledge into practical lifestyle changes that could fit into their every day life. Thus, walking speed and length of walk varied somewhat between participants. However, great care was taken to ensure that duration of the walks was similar and that all participants walked what they defined an ordinary slowly walking condition.

After finishing the cornflakes with milk meal, the participants were asked to walk in a comfortable slow speed that would mimic an ordinary slow walking situation. No special equipment (shoes or clothes) was required to participate in the experiments. The participants

walked on a flat footpath just outside the test room accompanied by project staff. Great care was taken to measure blood glucose levels at the correct intervals during the walks. For that purpose the participants stopped walking for less than 2 min allowing blood glucose measurement.

The subjective perceived exertion caused by 40 min walking was reported as “very light” (range 6 to 12, i.e. “extremely light” to “light”), according the Borg’s scale [113], with a mean value of 8 (“very light”).

## ORDER OF EXPERIMENTS

In the current studies all participants performed the same type of experiment on each particular experimental day, e.g. having a meal with post meal walking. In the current experiments only foods commonly used by the participants, and regular slow walking were evaluated. There was always at least 7 days between the experiments. We therefore believe that none of the interventions influenced the outcome response on later experimental days.

## MEASUREMENTS

### BLOOD GLUCOSE

Capillary blood glucose concentrations (mmol/L) were measured (Ascensia Contour, Bayer) before the meal and again at 15, 30, 45, 60, 75, 90, 105 and 120 min in the postprandial phase. As informed by the manufacturer, the glucometers from Bayer had a total error (system plus user error) of  $\leq 10\%$ , thus providing clinically and analytically acceptable results [118,119]. We nevertheless re-examined the variability. Using the same blood sample we determined the glucose concentration 10 times sequentially on each of 14 different Ascensia Contour apparatuses. After this test, we chose the three most accurate ones, which had intra assay coefficients of variation ranging from 2.2 to 2.3%

The average blood fasting glucose value was used as the basal value in the statistical calculations. The same apparatus/same person from the project staff was used to measure blood glucose on each participant all test days.

## BLOOD PRESSURE

Arterial blood pressure was measured in the sitting position at 0-time and again after 1h and 2h on each experimental day by the use of A&D Medical plus digital blood pressure monitor UA-767 (Tokyo, Japan).

## SATIETY

Immediately after each blood sample was collected, the subjects rated their subjective feeling of satiety using a 7 point category rating scale where 1 is very hungry and 7 is no hunger at all. Ratings were completed shortly after the blood samples were obtained.

## ANTHROPOMETRIC AND BLOOD MEASUREMENT DATA

Body weight was measured on the last experimental day. Data for age, height, waist circumference, blood pressure (except for group C), HbA<sub>1c</sub> and OGTT were collected on a separate day as part of the InnvaDiab-DEPLAN study [3] in which the subjects had participated.

## STATISTICAL ANALYSES

The primary outcome of this study was the overall postprandial glycemia, as estimated by several measures:

PV= postprandial blood glucose peak value

TTP= time to reach PV from zero time

IPV= incremental PV, i.e. PV minus the fasting blood glucose concentration

GP= glycemic profile, i.e. the duration of the incremental postprandial blood glucose response divided with the blood glucose incremental peak

IAUC= the Incremental Area Under the glucose vs. time Curve, calculated by the linear trapezoidal rule [120].

Data were analyzed using SPSS 15.0. All data were assessed for normal distribution of values. Comparison of mean values of normally distributed data within groups were performed by paired samples Student's t test. When appropriate, we also used non-parametric tests. For each group, a two-factor within-subject repeated measure ANOVA was used to test the effects of time and intervention, and the interaction between time and intervention.

## ETHICS

The studies were carried out according to the principles of the Helsinki declaration. As this was an extension of the originally planned InnvaDiab intervention, an extended approval was obtained by The National Committees for Research Ethics, Norway. All participants have given an informed written consent on their participation.

We used an interpreter to ensure that no language barriers prevented the participants from understanding the purpose of the experiments they were participating in, and that participation was voluntary.

Generally, participation in these experiments did not include any health risks except the small discomfort of blood sampling. However, we expected to find people who were at high risk of diabetes or CVD without knowing it themselves. All participants were given their own results, and we encouraged the participants to inform their physician if any values were found outside the 'normal' reference limits.

For the studies of PPG, up to 11 subjects participated simultaneously in the same experiment. During the 2h study period the participants had the opportunity to speak freely in their own language. Great care was taken to ensure the privacy of obtained results. However, the interpreter who was always in the room told us that the participants shared their results as matter for discussions. It was emphasized that sharing results was voluntary, but unfortunately, we do not know to what extent the participants felt forced to share personal information with other participants in the group. However, the participants repeatedly told us that they felt fortunate to participate in experiments that enabled them to translate knowledge of blood glucose regulation into practical lifestyle advices. They insisted that the discussions in the group of participants had enabled them to understand their individual PPG responses of different food/light physical activity.

This work has been funded by Idun Industrier AS. According to the signed agreement between University of Oslo and Idun Industrier AS, no limitations were put on publication of results, whatsoever found.

## MAIN RESULTS – SUMMARY OF PAPERS

### PAPER I

Lunde MSH, Hjellset VT, Holmboe-Ottesen G, Høstmark AT;

#### **Variations in postprandial blood glucose responses and satiety after intake of three types of bread**

*Journal of Nutrition and Metabolism*, vol. 2011, Article ID 437587, 7 pages, 2011.

doi:10.1155/2011/437587

**Aim:** - to study PPG and satiety after ingestion of breads with and without pea fibre and rapeseed oil.

**Methods:** Using a cross over design, 10 female Pakistani immigrants living in Oslo participated in experiments involving blood glucose measurements and ratings of subjective feeling of satiety every 15 min after intake of three types of bread.

**Results:** In response to ingesting 25 g CHO from regular coarse bread the blood glucose concentration increased gradually and reached a PV of 9.1 mmol/L after 45 min. Then, there was a gradual decrease to the initial value after 120 min. The postprandial blood glucose excursions, estimated by the peak value (PV), Incremental peak value (IPV) and glycemic profile (GP), were greatly attenuated after intake of a similar amount carbohydrate in fiber enriched bread (with or without rapeseed oil) as compared with regular coarse bread ( $p < 0.05$ ). IAUC in the time period 15 to 75 min after ingestion of bread was reduced by 30% after ingestion of pea fibre enriched bread (bread 2) ( $p < 0.05$ ). However, considering the whole 120 min experiment there were no significant group differences in IAUC. There was no difference between fibre enriched bread with or without rapeseed oil in PV, IPV or IAUC.

Using repeated measures ANOVA we found a significant main effect of time and type of bread ( $F = 30.7$  and  $24.7$  respectively,  $p < 0.001$ ), and an interaction between time and type ( $p < 0.005$ ).

Satiety ratings after intake of 25 g CHO in regular coarse bread was 7-23 % lower than corresponding ratings after intake of the other test meals and observed at all time points from 60 min and throughout the observation period ( $p < 0.05$  for all time points).



**Conclusion:** Breads containing a great percentage of pea fibre seem to blunt the rise in blood glucose while still keeping the satiety at a high level, but the apparent effects might partially be attributed to other components than pea fibre. No effect seems to be obtained by increasing the content of rapeseed oil in the pea fibre enriched bread.

## PAPER II

Lunde MSH, Hjellset VT, Høstmark AT;

### **Adjusting the amount and type of carbohydrate in a meal strongly reduced the post meal glycemic response in Pakistani immigrant women**

Submitted Journal of Diabetology, 2011

**Aim:** - to study PPG as influenced by changes in type and amount of CHO in a meal.

**Methods:** Using a cross over design, 20 female Pakistani immigrants living in Oslo participated in experiments involving blood glucose measurements every 15 min after intake of either cornflakes with milk, bread, or food with chick peas.

**Results:** A sustained elevated postprandial blood glucose concentration was found after intake of cornflakes providing 75g available CHO. When reducing the cornflake intake to obtain 25g CHO we found reductions in PV of 11% ( $p=0.008$ ) and IAUC of 51% ( $p=0.003$ ). IAUC was reduced by 40% ( $p=0.001$ ) in response to lowering the ingested amount of bread by 50%.

Postprandial blood glucose was also appreciably lowered after intake of 50g CHO as chick peas spiced with tomato and onion, compared to the same amount of available CHO as corn flakes with milk. Change to chick pea type of CHO resulted in a reduction in PV by 15.7% ( $p=0.0001$ ), and IAUC by 50.9% ( $p=0.0001$ ), and increased the time to reach PV (TTP), on average by 20 min ( $p=0.006$ ), and the glycaemic profile (GP) by 73.5%  $p=0.002$ . Glycemic responses on different days were positively correlated ( $r>0.9$ ,  $p<0.001$ ).

**Conclusion:** In diabetes prone subjects the PPG can be appreciably blunted both by reducing the quantity and changing the quality of the ingested carbohydrates. The study suggests that there are high- and low responders to a carbohydrate load, below the diabetes threshold.

### PAPER III

Lunde MSH, Hjellset VT, Høstmark AT;

#### **Slow postmeal walking reduces the blood glucose response– an exploratory study in female Pakistani immigrants**

Submitted Journal of Immigrant and Minority health 2011

**Aim:** - to study PPG and blood pressure as influenced by light post meal walking.

**Methods:** Using a cross over design, 11 female Pakistani immigrants living in Oslo were recruited to participate in three experiments where their blood glucose concentration was measured every 15 min, and the blood pressure was measured every hour, for 2h after intake of a high glycemic food (corn flakes with milk), either while resting after the meal or doing very light post meal walking of two durations.

**Results:** When resting after intake of 50 g CHO, the blood glucose concentration increased during the first 30 to 45 min, reaching a maximum value of 9.1 mmol/L after 45 min. Then the glucose concentration decreased but was still about one mmol/L higher than at baseline at the end of the experiment, i.e. at 2h. When 20 min very slow post meal walking was performed after intake of the same meal the mean PV was lowered by 8.2% (NS), and time to reach the PV was delayed, on average by 19 min ( $p=0.002$ ). These effects of walking were strengthened when the postprandial walk was increased to 40 min. In this latter experiment the time to reach PV from zero time (TTP) was delayed by 25 min ( $p=0.001$ ) and the PV was lowered by 16.3% ( $p=0.001$ ). Additionally, after postprandial walking, the blood glucose concentration approached baseline levels after 2h. Using repeated measures ANOVA we found a significant main effect of time and duration of light postprandial walk ( $F=26.8$  and  $6.9$  respectively,  $p<0.05$ ) and there was an interaction between time after the meal and duration of the walks ( $F=14.0$   $p<0.001$ ).

A significant 11% reduction ( $p<0.05$ ) in systolic blood pressure (SBP) was observed at 2h in the 40 min walking experiment as compared with 6% reduction (NS) on the control day (response difference,  $p<0.05$ ). No significant changes in corresponding values of the diastolic blood pressure were observed.

**Conclusion:** Very slow post meal walking after ingesting a high glycemic meal can appreciably reduce the rise in blood glucose, and also reduce the systolic blood pressure, as observed in female Pakistani immigrants living in Oslo.

## DISCUSSION

The results obtained in the present work suggest that simple lifestyle changes can appreciably reduce the post meal glucose concentration in these diabetes prone subjects.

## METHODOLOGICAL CONSIDERATIONS

A cross-over design was chosen to address the issues raised. In general, cross-over studies are useful to study improvements of symptoms in patients with chronic conditions such as IGT, but may be infeasible or unethical for studying rapidly changing conditions.

It was not possible to blind the intervention in the experiments. However, great care was taken by the project employees not to share any expectations of results during the experiments.

The primary strength of the cross-over design is that the influence of confounding covariates is reduced because each cross-over subject serves as his or her own control. In non-crossover studies, even in randomized ones, it may happen that different treatment-groups are found to be unbalanced on some covariates. Such imbalances are unlikely to occur in cross-over designed studies unless covariates were to change systematically during the study. For the present studies one could speculate whether the discomfort of blood sampling might give a psychological stress response that might increase the blood glucose levels. Furthermore, such an effect might be less pronounced as the participants got used to the measuring procedures, thereby leading to a between-experiments variation. We have no indications of such an effect in the present studies. Working against the hypothesis is the fact that the fasting blood glucose values in corresponding experiments were very similar. Furthermore, the participants were familiar with blood glucose measurements since they had previously been partaking in the InnvaDiab-DEPLAN study, involving two OGTT. Additionally, they were all familiar with the project staff and measurement procedures.

There are several issues that have to be considered to obtain high internal validity of the cross-over study. One important issue is to avoid any "carry-over" effects between treatments, which would certainly confound the estimates of the treatment effects. In practice, "carry-over" effects can be avoided with a sufficiently long "wash-out" period between treatments. In studies involving repeated carbohydrate intakes great care should be taken to avoid carry over effects on the postprandial blood glucose curves. It is well known that there is an improved carbohydrate tolerance after repeated glucose intakes, the Staub-Traugott effect, which in part seems to be caused by increased insulin response to repeated carbohydrate intakes [107].

However, the Staub-Traugott and other carry over effects are unlikely to take place under the conditions of the present work, in which there was as long as 7 days between the corresponding trials. On the other hand, variations in diet and physical activity during the last couple of days before each experiment could possibly influence the results. In an attempt to control for this, the participants were asked to behave as similarly as possible on the day before the experiments, and to fast for 12 hours before the experiments started each morning. Communication with the participants on experimental days gave the impression of good compliance with that requirement, and we do not consider that alterations in lifestyle during the trial period had a major influence on the outcome. However, one can not completely rule out that information bias might have occurred. Anticipating that there in theory could be variation in diet and physical activity on different days of the week, for each subject we chose to do all the experiments on the same day of the week.

There are also other threats to the internal validity of the cross-over design, namely a regression threat. When subjects are tested several times, their scores tend to regress towards the mean [121]. Regression toward the mean is not based on cause and effect, but rather on random error in a natural distribution around a mean. In many experiments it is difficult to control for the regression to the mean effect. Generally, when evaluating effect of any type of intervention, it may be hard to appreciate the relative contribution of the latter effect and a true biological effect.

A disadvantage of the repeated measure design is that it may not be possible for each participant to be present in all variations of the main experiment, and valuable information may be lost in the final analysis due to missing of results.

The sample size of the current studies was small, making the studies appear exploratory. In particular, the ability to generalize the findings is reduced; however, the cross over design of the study would reduce the measurement variability. A low number of subjects increase the risk of making Type II errors. However, the present results show, in general, large effects which would counteract such errors. Furthermore, several previous similar studies with a comparable small number of participants found highly significant effects of post meal light physical activity on the blood glucose responses [6,115,116]. Also in glycaemic index testing, using a crossover design, only ten subjects are regularly used [13,122]. Nevertheless, the low number of participants is a limitation concerning external validity. In the present study, PPG responses of diabetes prone female immigrant were evaluated, and the effect may not

necessarily be the same in healthy individuals. Also, ethnicity may be important for the explanation of the present results [92].

As shown by Høstmark et. al. postmeal blood glucose excursions can be attenuated by intake of a low glycemic food compared to intake of a high glycemic food [123] and by light post meal physical activity [6]. The present results suggest that similar responses can be obtained also in a group of Pakistani immigrant women that urgently need lifestyle advice for diabetes prevention.

All subjects in these studies had a waist circumference  $\geq 80$  cm which render it possible that the subjects suffer from the metabolic syndrome [124]. Since we did not determine fasting triglycerides and HDL in this study, we are not able to determine if the participants fall into the definition of the metabolic syndrome. Conceivably, attenuation of the postprandial glucose response should be accompanied by a lower insulin response [125], but we have no insulin data.

The rationale for conducting this study was to collect supporting data for practical lifestyle advice. It seemed therefore reasonable to study to what extent PPG might be influenced by “normal” mixed meals, and light post meal walking, so as to obtain practical intervention approaches, rather than elucidating mechanisms of action. Therefore, the main outcome of the present studies was the postmeal blood glucose responses. The postmeal blood glucose level is primarily governed by type and amount of ingested carbohydrate, the subsequent insulin secretion, tissue sensitivity to the circulating insulin, and is appreciably influenced by the rate of digestion and absorption of CHO in the intestine. The current experiments were however not designed to evaluate the relative contribution of any particular mechanisms of action that apply to the observed effects.

The harmful effects of postprandial hyperglycemia may partly be related to the production of free radicals. As shown by Ceriello et al., intake of a carbohydrate meal is followed by oxidative stress that is related to the level of hyperglycemia [89], and also to fluctuations in blood glucose levels [90,126,127]. Since we did not measure free radicals we have no data on the influence of the different interventions on oxidative stress, it is however tempting to speculate that the appreciable attenuating effect of the various treatments upon PPG might have reduced free radical production.

## DISCUSSION OF MAIN RESULTS

The discussion below will be divided according to the research questions raised in this thesis, all pertaining to a group of diabetes prone Pakistani immigrant women living in Oslo.

*To what extent will the PPG response to ingested carbohydrates be influenced by replacing some of the digestible carbohydrates in bread with pea fibre?*

As previously referred to, IDF has stated that it is important to reduce PPG [1], but will simple lifestyle modifications have such an effect? In Norway, bread is a major component of the diet and also Pakistani immigrants appreciate bread as a staple food [128]. Unfortunately, modern industry made bread is also a high glycemic type of food, raising the question of whether breads with a reduced glycemic potential can be made. Various attempts to reduce PPG have been reported, such as modifying the foods to obtain retarded digestion and absorption of carbohydrates [129], or increasing the secretion of regulatory hormones after a meal [130]. Previous studies have shown that inclusion of some types of dietary fibre can have an inhibitory effect on postprandial blood glucose elevation [131-133]. It seems, however, difficult to make palatable breads containing high amounts of fibre. However, as shown in the present work, pea fibre enrichment seems to be an exception. Indeed, replacing some of the digestible carbohydrates in bread with pea fibre appreciably attenuated the blood glucose elevation as compared with the post meal elevation after intake of regular bread.

Reducing the intake of refined carbohydrates and increasing fibre consumption has been prescribed by the American Diabetes Association as a strategy of for prevention of T2D [134]. Different fibres have, however, been shown to have different effects on postprandial blood glucose [110,135]. It has been reported previously that inclusion of whole yellow-pea flour compared to whole wheat flour in cakes and pasta attenuated the postprandial glycaemic response [111,136]. Since the present study compared two types of bread that differed not only in regard of the content of pea fibre, but also in regard of other types of fibre, we are not able to conclude that the blood glucose blunting effect of the pea fibre enriched bread was caused by pea fibre *per se*. For example, the regular bread contained wheat flour and whole meal wheat flour, whereas the pea fibre enriched bread contained wheat flour and ground whole rye. Rye tends to produce lower PPG with respect to wheat and the coarseness of the grind can also have an effect [137]. Additionally, the control bread contained dried sourdough of wheat, whereas the pea fibre bread contained dried sourdough of wheat and dried

sourdough from rye. Both rye, coarseness of grind, and sourdough have been found to lower PPG in various studies [138-140]. Thus, differences in post meal glycemia (or satiety) between the breads could partly have been caused by these differences. On the other hand, the pea fibre content was one major difference between the breads. We therefore have used the term “pea fibre enriched bread” as a descriptive term of bread containing a great percentage of pea fibre, with no allusion to a causal effect of pea fiber *per se*.

Both the peak glucose value (PV) and the incremental area under the glucose vs. time curves (IAUC) might be estimates of the glycation potential. In this work we did find a significant reduction in PV, and also a reduction in IAUC in the time period 15-75 min after intake of the pea fibre enriched bread as compared with control. In a comparable study, Vuksan et. al. recently reported reductions in IAUC as a result of increased fibre (i.e. *Salvia Hispanica* L.) in the ingested bread [141] and suggested that the decrease in postprandial glycemia might provide a potential explanation for improvements in cardiovascular risk factors observed after 12-week supplementation with *Salvia Hispanica* L., in type 2 diabetic subjects [142].

It would appear, therefore, that an increased percentage of fibre, including pea fibre, can blunt post meal blood glucose elevations. It is however difficult to assess whether the observed effects on PPG will be clinically interesting. Therefore, further studies are required to elucidate whether regular, long term use of pea fibre enriched bread might serve to prevent Type 2 diabetes and cardiovascular diseases. Previous epidemiological studies suggest however that the use of cereal fibre might reduce the risk of T2D [143-145] and cardiovascular diseases [146,147]. Foods high in dietary fibre are thought to reduce postprandial glucose responses by interfering mainly with glucose absorption [148].

The main dietary changes reported after migration among South Asians settled in Oslo are reduction in the fibre intake and increased consumption of processed carbohydrates and animal fats [96]. Thus, inclusion of pea fibre enriched bread in the habitual diet would seem a reasonable advice for this group.

*To what extent will inclusion of rapeseed oil in the fibre enriched bread influence the PPG response?*

Previous studies have suggested that fat may modify the rate of glucose absorption by delaying gastric emptying [149,150]. Recently, it has been reported that adding a fat component (rapeseed oil) or a protein component, either alone or together to a mashed potato based meal, resulted in decreased glycaemic responses [151]. Surprisingly, therefore,



inclusion of 9% fat in the pea fibre enriched bread did not alter the glycemic response. We have no data to explain these discrepancies, since the present study did not aim at exploring mechanisms of action. However, others have also reported only a modest reduction in postprandial blood glucose excursion caused by fat [152].

*To what extent will the satiety be influenced by using pea fibre enriched bread as compared with regular coarse bread?*

The findings in the present work suggest that satiety is more prolonged after intake of fibre enriched bread compared with ordinary coarse bread providing the same amount of CHO. As reviewed by Ludwig in 2000, also earlier studies seem to indicate increased satiety, and additionally, delayed return to hunger or decreased *ad libitum* food intake after low compared with high GI foods [153]. However, others have failed to support the hypothesis that a low glycemic diet suppresses hunger and/or increases satiety [154]. From the present study it is hard to distinguish between increased satiety caused by lowered glycaemic effect of pea fibre enriched bread and intake of an increased amount of the same bread required to obtain the same amount of available CHO.

It may be difficult to find objective measures of satiety. For example, when using categorical rating scales it may be difficult to understand the questions, and how to report the hunger sensation [155]. Many studies have been performed in order to explore the effect of delayed gastric emptying, rapid changes in blood glucose levels and hormones on satiety. In the present study we used a simple questionnaire to compare the subjective feelings of satiety after ingestion of three standardized bread meals. From our study, increasing the percentage of pea fibre seemed to have an effect both upon peak postprandial glucose levels and satiety. Accordingly, the present experiments suggest that addition of pea fibre to bread resulted in both low PPG and a sustained higher satiety rating.

To reduce body weight, lowered caloric intake has been prescribed, but low energy diets often imply a problem with hunger. It would appear that the findings in the present work might offer an alternative approach to counteract overweight, and possibly insulin resistance, i.e. regularly using pea fibre enriched bread. However, our study did not aim at studying weight reduction. Further studies are therefore required to elucidate this hypothesis. In favour of the hypothesis is a recent study in which it was concluded that reducing the glycemic load seemed to be an effective strategy to increase energy expenditure after a meal [156].

Thus, whereas there are several studies showing weight reducing effects of low glycemic diets [157-159], it seems that there is a lack of studies on low energy diets which at the same time give a high satiety, such as found after intake of the present pea fibre enriched, low glycemic bread.

We did no formal registration of palatability of the fibre bread, but none of the participants complained about using the breads. However, in a separate, as yet unpublished, study the palatability of the pea fibre enriched breads was reported to be good. Inclusion of pea fibre enriched bread would represent a small change in the diet, as the appearance of the bread is similar to other types of industrially baked regular coarse bread. Therefore, using this type of bread probably does not represent a major change in the eating habits, as is often seen for more special diets.

*To what extent will a moderate variation in type and amount of carbohydrates influence PPG?*

*Two experiments with altered **amount** of carbohydrate in the meal*

Conceivably, lowering of the amount carbohydrate ingested should lower PPG. The present results are in accordance with this view, but the variation in the mean blood glucose excursions in response to altering amount carbohydrate intake was surprisingly high. Unexpectedly, we found a sustained hyperglycemia for more than 2h after intake of corn flakes providing 75g available CHO. This was also the case in subjects with normal fasting blood glucose values. It would appear, therefore, that in some individuals, FBG might not reflect the carbohydrate tolerance. Furthermore, in subjects of the present study also a very low amount of carbohydrate (25g) gave an appreciable initial rise in the blood glucose concentration that was approximately similar to a two-fold higher carbohydrate intake (Paper II). These findings would seem to illustrate that the current participants have a very strong blood glucose response to ingested carbohydrates.

*An experiment with altered **type** of carbohydrate in the meal*

There is a large body of evidence that some types of carbohydrates have a low glycemic effect. In fact, the glycemic index (GI) concept was introduced by Jenkins et al already in 1981 [108] to quantify and range the glycemic effect of various foods, but, the use of GI in the clinical practice has been questioned [160]. The variance of GI may be very high and some foods with a high GI, e.g. carrots, would have to be ingested in unrealistic high amounts

to exert a high glycemic effect. Moreover, co-ingestion of other food ingredients e.g. acetic acid seems to modify the glycemic effect [161]. Nevertheless, the GI concept is widely accepted as a tool to classify the glycemic impact of various foods.

In accordance with previous studies [162], also in the present work chick peas gave an appreciably lower blood glucose response as compared with a similar amount of carbohydrates given as cornflakes or bread. This would be beneficial to individuals seeking glycaemic control through their diets. Insoluble fibre may cause reductions in postprandial hyperglycemia [163], and can be found in high amounts in chick peas [164]. In addition, chick peas contain protein [164] which may stimulate the insulin secretion [165].

*To what extent will there be variations between subjects in PPG after intake of the same amount of carbohydrates, i.e. high and low responders to ingested glucose, among subjects with normal fasting blood glucose concentration?*

The present work suggests that subjects with a high blood glucose response in one meal experiment would also have increased PPG responses in other, similar experiments. By definition, patients with diagnosed diabetes will respond stronger to a glycaemic load than healthy subjects. However, the present results indicate that there might be high- and low responders to a carbohydrate load even below the diabetes threshold. These findings are in line with a previous suggestion by Høstmark et. al. [123] that there are high- and low responders to a glucose load, and that high responders possibly may have a special benefit of ingesting carbohydrates with a low glycemic load. However, the determination of GI has been found to be largely unaffected by subject characteristics [125]. On the other hand, and of interest for the interpretation of the results in the present study, are the findings recently published by Dhaheri et. al. that GI values of foods are affected by body composition and ethnicity [166]. Nevertheless, our data suggest that the potential for a high glycaemic response after CHO intake is a characteristic of each single person.

*To what extent will very slow postmeal walking attenuate the post meal blood glucose response?*

Previous studies in healthy ethnic Norwegian men and women have shown that light post meal physical activity can blunt the rise in blood glucose after carbohydrate intake [6,115,116]. However, the physical activity regularly performed by the present diabetes prone subjects was very low [5], and consisted of very slow walking. This raises the question of whether this type of very low intensity physical activity could possibly have a similar effect.

Diabetes prone subjects are generally encouraged to increase the level of physical activity to achieve good blood glucose control, but not specifically by encouraging slow post meal walking. However, as shown in the present work also slow walking after a carbohydrate meal strongly attenuated the blood glucose elevation. It would appear, accordingly, that regular practising such walking could be an efficient approach to counteract meal related hyperglycaemic episodes, and possibly in the long term improve the general glycemic control in diabetes prone subjects. However, further long term studies are required to corroborate this assumption.

Our study did not explain the physiological mechanisms involved in the effects of walking on blood glucose. Among potential explanations of the glucose lowering effect of physical activity is increased stimulation of GLUT-4 translocations to the cell membrane, thereby facilitating glucose transport into the cell. It is well established that there are two distinct intracellular pools of glucose transporters in skeletal muscle, one responding to exercise and another responding to insulin [167]. It would therefore seem that insulin resistant subjects could have special benefit of doing light physical activity to attenuate the glucose elevations after carbohydrate rich meals.

*To what extent will very slow post meal walking attenuate the blood pressure?*

In this study we found that an acute exercise session promoted the lowering of systolic blood pressure during the post exercise period. In line with Lima et al. [168] we found that even slow walking lowered systolic blood pressure. Furthermore, in line with Mach et al. [169] only the longest duration of light post meal physical activity gave a reduction in blood pressure. Among possible mechanisms involved in the regulation of short term arterial blood pressure are activity of autonomic nerves, concentration of hormones (e.g. epinephrine, angiotensin II, vasopressin), or other vasoregulatory components such as nitrogen oxide. However, the present study did not aim at clarifying mechanisms of action.

Walking seems to be a beneficial form of physical activity for diabetics [170]. The present results strongly suggest that low intensity post meal walking may represent a "low barrier" lifestyle advice that could have an appreciable preventive potential, if regularly performed. Further studies are however needed to substantiate this hypothesis, and to clarify the optimal work duration and intensity required to blunt the post meal glucose elevation.

#### SOME ADDITIONAL CONSIDERATIONS

We observed that the subjects seemed to increasingly understand the purpose of the various experiments as they went through them. Thus, participation in this type of study seemed suitable to enable the subjects to obtain and translate knowledge about blood glucose regulation into a practical lifestyle change that possibly might be of relevance to reduce the risk of diabetes, but further studies have to be done to substantiate this hypothesis.

Postprandial responses to intake of two types of pulses, i.e. yellow pea (the hull part) and chick peas, have been given attention in this thesis. The attenuation in PPG seen after intake of pulses is in line with the findings in a systematic 2009-review and meta-analysis where Sievenpiper [171] concluded that dietary non-seed pulses can improve the glycaemic control when used alone, or in combination with other dietary interventions to increase the fibre of the diet.

#### SUGGESTED CLINICAL RELEVANCE

The International Diabetes Federation (IDF) recommends management of the blood glucose levels by addressing both the fasting blood glucose concentration and post meal glucose levels. The guideline recommend that PPG should not exceed 7.8 mmol/L during the 2 h post meal period [1]. Others have suggested slightly differing threshold values.

Accordingly, there is substantial interest in dietary and pharmacological strategies directed to the control of postprandial blood glucose excursions. As indicated in the present study, a significant step to achieve this goal seems to be rather small lifestyle changes, i.e. either by increased use of low glycemic carbohydrates, such as chickpeas [172], by reducing the CHO intake in each meal, or by performing post meal light walking. The reductions obtained by these interventions are of the same order of magnitude as obtained by use of  $\alpha$ -glucosidase inhibitors [173]. Therefore, a combination of all three approaches should be encouraged.

Fasting plasma glucose and HbA<sub>1c</sub> are the most commonly measured glycemic variables. However, these variables do not seem to completely reflect the glycemic control, and should be supplemented by measurement of glucose variability [174], as e.g. assessed by the incremental area under the glucose vs. time curve (IAUC). A standardized IAUC measurement of postprandial glucose requires however oral glucose tolerances test (OGTT), which unfortunately seems unrealistic to carry out on a population basis. In our experience, repeated measurements of the blood glucose concentration, for example during one hour after a common carbohydrate meal may be easier to perform, even by self-monitoring.

There seems to be a wide variability between subjects in terms of glycemic responses to particular foods. An important public health strategy should accordingly be to encourage people to be aware of their own tolerance of carbohydrates, as well as informing about the importance of keeping the blood sugar within a narrow range. Dietary information should be given so as to enable people to design their diet to limit the post meal glucose excursions. These recommendations are in line with recommendations from an Asian-Pacific expert panel which encourages increased screening for PPG among Asian adults who are overweight and have additional risk factors such as IGT, CVD, hypertension, dyslipidemia or a sedentary lifestyle. In the absence of the above criteria the expert committee recommends that PPG screening should begin at the age of 45 years and further addresses the importance of blood glucose management in the postprandial period [175].

It is generally assumed that there are a large number of people having IGT without knowing it. As shown in the present work, even minor lifestyle changes may appreciably reduce blood glucose excursions in IGT individuals. Hypothetically, small lifestyle change aiming at reduction of post meal glucose elevations in the general population could possibly reduce the prevalence of diabetes, but this suggestion has to be proven.

#### FURTHER RESEARCH

There is growing body of evidence on the importance of addressing PPG for prevention of T2D and CVD [176]. It remains however to be shown whether habitually practising PPG lowering by the methods studied in this thesis would have an effect to prevent these diseases. It is also under debate whether a patient with very variable glucose levels is at higher risk of micro- or macrovascular complications than someone having the same mean glucose concentration, but with fewer fluctuations in the blood glucose levels [177,178]. Further studies are therefore needed to establish the long term potential of regularly reducing postmeal glucose excursions and to clarify the optimal postmeal blood glucose levels related to lifestyle diseases.

#### SUGGESTED IMPLICATIONS FOR POLICYMAKERS

Healthy diet and physical activity are cornerstones for prevention of lifestyle diseases. An important public health strategy could be to increase the number of available processed carbohydrate-rich foods with a lower glycemic potential than their regular counterparts. The present study would seem in support of the general hypothesis that inclusion of fibre is

beneficial for improved blood glucose control, keeping in mind that other differences than pea fibre enrichment might contribute to explain our findings.

Today dietary advice includes a high proportion of CHO in the habitual diet. In that perspective it is important to take into account the type of the carbohydrates, especially when the total carbohydrate intakes are at the upper end of the recommended range. There is a broad consensus to recommend wholegrain cereals, fruits, vegetables and legumes. However, as shown in the present work, post meal blood glucose excursions may be above IDF recommendations after only small meals when high glycemic foods, such as regular coarse bread, are consumed. Indeed, the diabetes prone subjects of the present study exceeded IDF recommendations after only 1.5 slices of ordinary coarse bread. This observation raises the question of whether - in the future - dietary advice should be given on an individual basis according to the glucose tolerance status.

Finally, it seems pertinent to remember that IDF's "Call for action on diabetes" from 2010 points out that the **"time to translate evidence into practice for diabetes is NOW."**

## CONCLUSION:

Based upon results obtained in a group of diabetes prone female Pakistani immigrants, it seems that:

1. -breads containing a great percentage of pea fibre can appreciably blunt the rise in blood glucose, but the apparent fibre effects might partially be attributed to other bread components than pea fibre per se.
2. -inclusion of 9% rapeseed oil in the fibre enriched bread may not influence PPG significantly.
3. -the satiety can be prolonged by using pea fibre enriched bread compared to regular with coarse bread providing the same amount of available CHO.
4. -PPG can be appreciable reduced by moderately reducing the quantity, and changing the quality of ingested carbohydrates.

5. -there is a great variation between subjects in PPG after intake of similar amount/type of carbohydrate meals, among subjects with fasting blood glucose concentration below the diabetes threshold.
6. -very slow post meal walking after ingesting a high glycemic meal can appreciably reduce PPG, and also reduce the systolic blood pressure.

These observations might offer a basis for practical lifestyle advice to reduce PPG, and in the course of time possibly also contribute to prevent some lifestyle diseases, but this latter suggestion would have to be substantiated by further studies.



## REFERENCE LIST

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## Research Article

# Variations in Postprandial Blood Glucose Responses and Satiety after Intake of Three Types of Bread

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Received 18 November 2010; Revised 7 March 2011; Accepted 5 April 2011

Academic Editor: S. Samman

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**Background.** The magnitude and duration of postprandial blood glucose (PPG) elevations are important risk factors of diabetes and coronary heart diseases. **Aim.** To study PPG after ingestion of breads with and without pea fibre and rapeseed oil. **Methods.** After fasting overnight, 10 Pakistani immigrant women participated in three experiments having a crossover design and involving ingestion of various types of bread: regular coarse bread or fibre enriched-bread with two levels of rapeseed oil, all providing 25 g available carbohydrates (CHO). Blood glucose and satiety were determined before the meal and every 15 min over the next 2 hours. **Results.** Intake of an amount of pea fibre-enriched bread containing 25 g CHO attenuated, the postprandial peak glucose value, the incremental area under the glucose versus time curve during 15 to 75 min, and the glycemic profile, and increased duration of satiety ( $P < .05$ ), as compared with intake of regular bread with 25 g carbohydrate. **Conclusion.** Pea fibre-enriched breads can reduce PPG and prolong satiety.

## 1. Background

The burden of cardiovascular diseases (CVD), obesity, and diabetes is rapidly increasing worldwide [1–3]. Disturbances in blood glucose levels are implicated in the development of these diseases [4]. Normally, the blood glucose concentration is well regulated by hormones, such as insulin and several counterregulatory hormones, but many external factors such as physical activity [5], emotional status, [6] and diet [7] will also modify the blood glucose levels.

In particular, the postprandial blood glucose concentration appears to play a critical role in progression of diabetes and CVD [8, 9]. In a meta-analysis of observational studies from 2008, Barclay et al. [10] found that postprandial hyperglycemia contributes to chronic disease, independently of diabetes status. Benefits of reducing PPG levels have been demonstrated in connection with chronic diseases in general [11] and for CVD [9, 12], diabetes, and obesity [4, 13] in particular. It seems accordingly of special importance to avoid sustained hyperglycaemic episodes and large blood glucose fluctuations during the day. Since the highest glucose levels

occur in the postprandial period, glycaemic control in this period is important, especially after ingestion of high glycaemic foods (e.g., certain types of bread).

Postprandial blood glucose is largely influenced by the carbohydrate load of the meal implying that diets with low glycaemic loads are beneficial in controlling postmeal plasma glucose [7]. Several studies have suggested that the blood glucose fluctuations are associated with oxidative stress and inflammation [14–16]. The term glycemic profile (GP) has been introduced defined as the duration of the incremental postprandial blood glucose response divided with the blood glucose incremental peak (min/mM) [17].

GL of a meal can be lowered either by reducing amount ingested and/or by reducing the GI of the meal. The latter can for example be achieved by using fibre-enriched foods [7]. It is well known that both the type and amount of carbohydrates can modify the postprandial glucose levels [18]. Fibre is often categorized as soluble or insoluble ones. Intake of soluble fibre may result in formation of health-promoting compounds during fermentation in the large bowel whereas insoluble fibres increases and softens the stool bulk, thereby

shortening the transit time through the intestinal tract [19]. In addition, fibre may have the ability to bind bile acids and decrease reabsorption of bile acids and cholesterol from the intestine.

Since dietary fibre seems to have a beneficial influence on glucose homeostasis, it is generally recommended that people should be encouraged to increase their fibre consumption, for example, from whole grains [20]. However, inclusion of fibre and whole grains seem to complicate the industrial production of bread.

Pea fibre has traditionally not been a common ingredient in bread recipes. It is, however, known that intake of whole peas will influence blood glucose level [7]. Accordingly, replacing available carbohydrates in breads by pea fibre may potentially reduce the glycemic impact of such breads. In 2009, Marinangeli et al. concluded that whole yellow-pea flour can be used to produce low glycemic functional foods possessing sensory attributes that are comparable to identical food products containing whole-wheat flour [21]. The baking industry in Norway has recently succeeded in making pea fibre-enriched bread without compromising the bread production methods.

There are large intraindividual differences in the population in regard to postprandial levels of blood glucose after intake of carbohydrates. Progression towards type 2 diabetes manifests as a gradual deterioration of postprandial blood glucose control. These differences in blood glucose are most pronounced after ingestion of food that has the potential to increase blood glucose the most, that is, a meal with high glycemic load. There may be ethnic differences in the glycemic response to carbohydrates. Dickinson et al. [16] found that the postprandial hyperglycemia and insulin sensitivity varied among different ethnic groups, and that lean, young South East Asians had the highest postprandial glycemia and the lowest insulin sensitivity in response to a realistic carbohydrate load.

The first aim of the present work was to examine to what extent the PPG response might be attenuated by replacing some of the digestible carbohydrates with pea fibre. When comparing PPG responses to these breads, great care was taken to ensure that equal quantities of available carbohydrates were ingested, but different amount of fibre. Secondly, since ingestion of fat with carbohydrates has previously been reported to favorably reduce PPG [22, 23], we also studied whether inclusion of rapeseed oil to the fibre-enriched bread recipe would influence the PPG response. Again, great care was taken to ensure that the ingested amount of available carbohydrates were similar in breads with different amounts of rapeseed oil. Thirdly, we wanted to evaluate the satiety after ingestion of the different types of bread.

## 2. Methods

**2.1. Ethics.** The study was carried out according to the Helsinki declaration and was approved by The National Committees for Research Ethics, Norway, 2.2008.2456. Participants gave informed and written consent.

TABLE 1: Baseline characteristics of the participants.

	Mean	SD
Age (years)	46	7.9
BMI (kg/m <sup>2</sup> )	31.0	5.0
Waist circumference (cm)	96.8	12.2
Blood pressure (systolic/diastolic) (mmHg)	120/82	16.7/10.9
Fasting blood glucose (mmol/L)*	5.6	0.5
Fasting blood glucose (mmol/L)**	5.6	0.2
2-h blood glucose value (mmol/L)** (OGTT)	8.3	1.9

\* Mean value of 9 measurements (3 measurements each of the 3 experimental days).

\*\* Mean value of 3 measurements performed during the OGTT.

**2.2. Subjects.** The 10 participants were recruited from the InnvaDiab-DEPLAN lifestyle intervention study among female Pakistani immigrants living in Oslo with a high risk of developing type 2 diabetes [24]. Five participants had impaired glucose tolerance following an oral glucose tolerance test (OGTT) with blood glucose concentration above 7.8 mmol/L 2 h after glucose ingestion. Baseline data for the participating subjects are presented in Table 1. Mean age of the participants was 46 years (range: 30 to 59), and mean body mass index (BMI; kg/m<sup>2</sup>) 31.0 (range: 25.7 to 41.9). The average glycated hemoglobin (HbA<sub>1c</sub>) value was 5.6% (range: 4.9 to 6.1). Fasting blood glucose measured on the three experimental days was 5.6 (range: 4.7 to 6.7). All participants had waist circumference  $\geq 80$  cm. These immigrants have adapted to Western eating habits [25], of which Norwegian leavened whole-wheat bread is a major component. Subjects on glucose-lowering medication were excluded from the study.

**2.3. The Breads.** Three types of bread were tested in this study, and all were baked, cooled, and frozen according to a standardized procedure at Idun Industries (Idun, Norway), and the baking process was the same for all breads. The physical characteristics, that is, colour, crust firmness, specific volume, and the sensory properties of the breads were kept as similar as possible.

The content of available carbohydrates, total starch, and dietary fibre was provided by the manufacturer, and based upon calculations.

All the loaves were for the most part based on wheat flour, and for the fibre-enriched breads the main fibre source used was pea hull fibre. The chemical profile of the pea hull fibre is 85–90% of dietary fibre (approx. 1/6 of soluble/insoluble fibre), 10–15% of protein/starch/fat/oligosaccharides, and simple sugars.

The content of bread was as follows in falling order.

**Regular Coarse Bread, Bread 1 (Low Fibre, Low Fat).** Water, wholemeal wheat flour, wheat flour, yeast, margarine (vegetable oil), water, salt, hydrogenated vegetable fat, emulsifier (E471), acidity regulator (E330), flavour, salt, wheat gluten, wholemeal rye, dried sourdough of wheat, rapeseed oil, and enzymes.



TABLE 2: Portion sizes and contents of bread tested.

	Bread types					
	Bread 1		Bread 2		Bread 3	
	(low fiber, low fat)		(high fiber, low fat)		(high fiber, high fat)	
Portion size						
g bread	61		119		133	
(corresponding g CHO)	(25 g CHO)		(25 g CHO)		(25 g CHO)	
Content	Per100 g	Per portion	Per 100 g	Per portion	Per 100 g	Per portion
Energy (kcal)	220	135	145	173	200	266
Dietary fibre (g)	4.6	2.8	17	20.2	17	22.6
Protein (g)	8.7	5.3	12	14.3	11	14
Carbohydrate minus fibre (g)	40.1	25	21	25	19	25
Fat (g)	2.8	1.7	1	1.2	9	12

*Fibre-Enriched Bread, Bread 2 (High Fibre, Low Fat).* Water, wheat flour, pea fibre, wheat gluten, barley, yeast, dried sourdough from wheat, salt, alginate, pectin, dextrose, oat, dried sourdough from rye, emulsifier (E472e), ground whole rye, rapeseed oil, ascorbic acid (E300), and enzymes.

*Fibre-Enriched Bread, Bread 3 (High Fibre, High Fat).* Water, wheat flour, pea fibre, rapeseed oil, wheat gluten, yeast, dried sourdough from wheat, salt, alginate, pectin, dextrose, oat, dried sourdough from rye, emulsifier (E472e), ground whole rye, ascorbic acid (E300), and enzymes.

The breads varied in content of energy, macronutrients, and dietary fiber.

Bread 1, per 100 g: 220 kcal, 4.6 g fibre, 8.7 g protein, 40.1 g CHO (minus fibre), and 2.8 g fat.

Bread 2, per 100 g: 145 kcal, 17 g fibre, 12 g protein, 21 g CHO (minus fibre), and 1 g fat.

Bread 3, per 100 g: 200 kcal, 17 g fibre, 11 g protein, 19 g CHO (minus fibre), and 9 g fat.

**2.4. The Meals.** Sliced bread, if preferred toasted, was served with 200 mL of tap water. We calculated portion sizes so as to obtain 25 g available carbohydrate. Data for macronutrient composition, including available carbohydrate and dietary fiber, was provided by the manufacturer. The portion sizes are shown in Table 2. Great care was taken to ensure that equal quantities of available carbohydrates were ingested.

**2.5. Experimental Procedures.** On separate days and after an overnight fast, 10 subjects participated in three experiments, in a randomized crossover design. On experimental days, the subjects arrived at 0845 hrs and sat resting until 0900 hrs. At that point, the fasting blood glucose concentration was measured in triplicate, and subsequently one test meal of bread was served. The subjects consumed the bread in a comfortable place within 15 min. The postmeal blood glucose concentration was measured repeatedly during a 2-hour period after the start of the test meal. The test meals were consumed in random order on separate mornings with one week between subsequent sessions.

**2.6. Anthropometric and Blood Measurement Data.** Body weight was measured on the last experimental day. Data for age, height, waist circumference, blood pressure, HbA1c, and OGTT were collected on a separate day as part of the InnvaDiab-DEPLAN study [24] in which the subjects had participated.

**2.7. Pre- and Postprandial Blood Sampling and Blood Glucose Measurements.** Capillary blood glucose concentrations (mmol/L) were measured (Ascensia Contour, Bayer) before the meal and again at 15, 30, 45, 60, 75, 90, 105, and 120 min in the postprandial phase. As informed by the manufacturer, the glucometers from Bayer had an accuracy of  $\leq 10\%$  thus providing clinically and analytically acceptable results [26, 27]. The blood glucose concentration before each meal (time = 0) was measured  $\times 3$ , and the average value was used as the basal value in the statistical calculations. The same apparatus was used to measure blood glucose on each participant all test days.

**2.8. Satiety.** Immediately after each blood sample was collected, the subjects rated their subjective feeling of satiety using a 7-point category rating scale where 1 is very hungry and 7 is no hunger at all. Ratings were completed shortly after the blood samples were obtained.

**2.9. Statistical Methods.** The primary outcome of this study was the overall postprandial glycemia, as estimated by several measures:

PV: postprandial blood glucose peak value,

TTP: time to reach PV from zero time,

IPV: incremental PV, that is, PV minus fasting blood glucose,

GP: glycemic profile, that is, the duration of the incremental postprandial blood glucose response divided with the blood glucose incremental peak,

IAUC: the incremental area under the glucose versus time curve, calculated by the linear trapezoidal rule (WHO 1997).

TABLE 3: Various measures of the glycemic response after ingestion of different types of bread.

Glycemic measure	Bread 1 (low fat, low fiber)	Bread 2 (low fat, high fiber)	Bread 3 (high fat, high fiber)
	25 g CH	25 g CH	25 g CH
PV (mmol/L)	9.2 ± 0.4 <sup>a</sup>	8.0 ± 0.2	7.6 ± 0.3
TTP (min)	47 ± 4	48 ± 5	52 ± 4
IPV (mmol/L)	3.6 ± 1.1 <sup>a</sup>	2.4 ± 0.7	2.0 ± 0.6
GP (min/mmol/L)	28.9 ± 9.2 <sup>a</sup>	48.5 ± 14.0	60.6 ± 18.3
IAUC (mmol × L <sup>-1</sup> × min)	177.6 ± 23.2	143.1 ± 16.8	134.6 ± 17.4

PV: average postprandial blood glucose peak value; TTP: time to peak value, IPV: incremental peak; GP: and glycemic profile; IAUC: incremental area under the 120 min glucose concentration versus time curve (IAUC).

<sup>a</sup> $P < .05$  versus Bread 2 and 3.

Data was analyzed using SPSS 15.0. All data were assessed for normal distribution of values. Comparison of mean values of normally distributed data within groups were performed by paired samples Student's *t*-test. For each group, a two-factor within-subject repeated measure ANOVA was used to test the effects of time and type of bread, and the interaction between time and type. Data are reported as mean values ± SEM in figures, or mean with SD in text and tables. When appropriate, the results were adjusted for baseline values.

### 3. Results

The fasting blood glucose level was  $5.6 \pm 0.6$  mmol/L all three test days.

**3.1. Postprandial Blood Glucose Response to Different Types of Bread.** In response to ingesting 25 g CHO from Bread 1 the blood glucose concentration increased gradually and reached a peak value of 9.1 mmol/L after 45 min (Figure 1). Then there was a gradual decrease to the initial value after 120 min. Average blood glucose curves had the same qualitative time course after ingestion of fibre-enriched bread, but the postprandial glucose excursions, estimated by PV, IPV, and GP, were attenuated by Bread 2 and 3 as compared with Bread 1 ( $P < .05$ ). Considering the whole 120 min experiment, there were no significant group differences in IAUC. However, IAUC in the time period 15 to 75 min after ingestion of bread was significantly reduced after ingestion of pea fibre-enriched bread ( $P < .05$ ). There was no difference between Bread 2 and 3 in PV, IPV, and IAUC, Table 3.

Using repeated measures ANOVA, we found a significant main effect of time and type of bread ( $F = 30.7$  and  $24.7$ , resp.,  $P$ -value  $< .001$ ) and an interaction between time and type ( $P < .005$ ).

**3.2. Satiety.** For all experiments, the average zero point satiety was rated between 4 and 5 and increased as the participants consumed the bread during the first 15 min (Figure 2). The satiety levelled off after 15 min and was sustained during the trial period after ingestion of 25 g CHO as fibre-enriched bread with 9% fat. The mean satiety decreased 45 min after intake of 25 g CHO ingested in regular

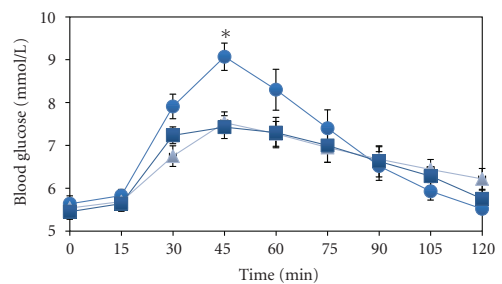


FIGURE 1: Blood glucose concentration as influenced by intake of various types of bread. On separate days and after an overnight fast, the blood glucose concentration was determined after ingestion of three types of bread which were given in portions providing 25 g carbohydrates,  $n = 10$ . Total weight of the breads varied, being 61 g for Bread 1, which is regular coarse bread (closed circles), 119 g for Bread 2 which is bread with 17% pea fibre and 1% rapeseed oil (squares), and 133 g for Bread 3 containing 17% pea fibre and 9% rapeseed oil (triangles). Mean values ± SEM. Note broken y-axis. \* $P < .05$  versus corresponding value when ingesting pea fibre-enriched bread.

coarse bread. By contrast, only a slight decrease in satiety was observed even 75 min after intake of 25 g CHO ingested in fibre-enriched bread with 1% fat. The subjectively rated satiety values after intake of 25 g CHO in regular coarse bread (bread 1) was significantly different from the other test meals at all time points from 60 min and throughout the observation period ( $P < .05$  for all time points). Corrections for variations in baseline values did not change the outcome. It seems accordingly that under the conditions of this study the amount of ingested bread, rather than amount of carbohydrates or energy governs the level of satiety.

### 4. Discussion

Previous studies have shown that fibre can lower postprandial glycemia [28, 29]. It seems, however, difficult to make acceptable breads containing high amounts of fibre, but pea fibre enrichment seems to be an exception. The present study

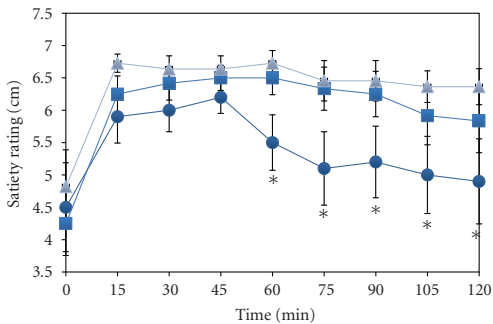


FIGURE 2: Satiety rating in the time period after intake of various amounts and types of bread. On separate days and after an overnight fast, 10 subjects rated their satiety during two hours after ingestion of various amounts and types of bread: triangles = pea fibre-enriched bread containing 25 g carbohydrate with 9% rapeseed oil; squares = pea fibre-enriched bread containing 25 g carbohydrate and 1% rapeseed oil; circles = regular coarse bread containing 25 g carbohydrate. Satiety was rated on a 7-point scale where 1 is very hungry and 7 completely satisfied. Mean values  $\pm$  SEM. Note broken y-axis. \* $P < .05$  versus corresponding value when ingesting same amount of available CHO as pea fibre-enriched bread.

demonstrates that replacing some of the digestible carbohydrates in bread with pea fibre can appreciably reduce blood glucose elevation after intake of such bread. Therefore, regular intake of pea fibre-enriched breads could be a useful approach to counteract high excursions of blood glucose. Additionally, inclusion of pea fibre seems to allow the subjects to eat a satisfying quantity of bread, maintaining satiety high over a longer period, and at the same time keeping the postprandial blood glucose levels significantly lower than after intake of the control bread. The participants of this experiment were not asked if they found the breads palatable, but none of them complained about ingesting the breads. Additionally, in a separate, yet unpublished, study the palatability of the pea fibre-enriched breads was reported to be good. Inclusion of pea fibre-enriched bread would represent a small change in the diet as the appearance of the bread is similar to other industrial baked regular coarse bread and do not represent a major change in eating habits as often seen for more special diets.

We emphasize that our data are not sufficient to conclude that it is the pea fibre *per se* which causes the reduced postprandial glycemia. Thus, the control bread and the pea fibre bread contained different ingredients other than just the pea fibre. For example, the regular bread contained wheat flour and whole meal wheat flour whereas the pea fibre-enriched bread contained wheat flour and ground whole rye. Rye tends to produce lower PPG with respect to wheat and the coarseness of the grind can also have an effect [30]. Additionally, the control bread contained dried sourdough of wheat whereas the pea fibre bread contained dried sourdough of wheat and dried sourdough from rye. Rye, coarse-

ness of grind, and sourdough have been found to lower PPG in various studies [31–33]. Thus, differences in postmeal glycemia (or satiety) between the breads could partly be attributed to these differences. Nevertheless, the major difference between the breads was the pea fibre content. We therefore have used the term “pea fibre-enriched bread” as a descriptive term of bread containing a great percentage of pea fibre, with no allusion to a causal effect of pea fiber *per se*. It is widely accepted that repeated, high postprandial levels of blood glucose have a negative impact on health. The harmful effects of postprandial hyperglycemia may partly be related to the production of free radicals. As shown by Ceriello et al., intake of a carbohydrate meal is followed by oxidative stress that is related to the level of hyperglycemia [34], and to fluctuations in blood glucose levels [14, 16, 35]. In our study we did not measure free radicals. It is therefore impossible to assess the influence of pea fibre-enriched bread on these variables, but it is tempting to speculate if the appreciable attenuating effect upon PPG could reduce free radical production.

The incremental area under the glucose versus time curve (IAUC) is probably an appropriate indicator of the glycation potential. In this work we did find a significant reduction of IAUC in the time period 15–75 min after intake of the pea fibre-enriched bread as compared with control. However, the IAUC for the entire 2-hour period did not differ significantly between the experiments. In this context there might have been a power problem, and the possibility of making a Type 2 error should be considered. However, coingestion of pea fibre attenuated the postprandial blood glucose response as estimated by PV, and hence presumably also lowered the glycation potential. Vuksan et al. have recently reported reductions in IAUC as a result of coingestion of whole grain (*Salvia Hispanica* L.) baked into with bread [36].

To reduce body weight, lowered caloric intake has been prescribed. There is, however, a problem with hunger when using low-energy diets. Measurements of complex sensations such as hunger is difficult and one concern with categorical rating scales is that the lack of clarity on how to understand the questions and how to report complex sensations [37]. Nevertheless, our data show that addition of pea fibre to bread resulted in both low PPG and a higher satiety rating. Thus, this could seem to offer an alternative approach to counteract overweight and possibly insulin resistance. Further studies are, however, required to corroborate this hypothesis. In favour of the hypothesis is a recent study in which it was concluded that reducing the glycemic load of a meal by lowering the glycemic index seemed an effective strategy to increase energy expenditure after a meal [38].

There might be great differences in digestibility and absorbability of different types of carbohydrate-rich foods, resulting in great variation in their PPG effects. The present results strongly suggest that high PPG and large blood glucose fluctuations during the day can be counteracted by using pea enriched bread instead of the regular types of coarse bread baked with more than 50% wholegrain without any additional fibre sources.

The use of carbohydrate-rich foods manifests differently in different cultures around the world. Nevertheless, inclusion of such foods prepared according to different local recipes is common. Refined high GI products are often cheap, easily accessible, and palatable. An important public health strategy could be to increase the number of available processed carbohydrate-rich foods with a lower glycemic potential than their regular counterparts. The present study would seem in support of the general hypothesis that inclusion of fibre is beneficial for improved blood glucose control, keeping in mind that other differences than pea fibre-enrichment might contribute to explain our findings.

Surprisingly, inclusion of 9% fat in the pea fibre-enriched bread did not alter the glycemic response. Previous studies have suggested that fat may modify the rate of glucose absorption by delaying gastric emptying [39]. However, this study did not aim at exploring the different mechanisms involved in the observed effects.

It may be difficult to find objective measures of satiety. Many studies have been performed in order to explore the effect of delayed gastric emptying and rapid changes in blood glucose levels and hormones on satiety. In the present study we used a simple questionnaire to compare the subjective feelings of satiety after ingestion of three standardized bread meals. From our study, increasing the percentage of pea fibre had an effect both upon peak postprandial glucose levels and satiety.

All the subjects in this study had a waist circumference  $\geq 80$  cm, which render, it possible that these subjects suffer from metabolic syndrome [40]. Since we did not include determination of fasting triglycerides and HDL in this study, we are not able to evaluate if the participants fall into the definition of the metabolic syndrome. Also the lack of insulin data represents a limitation of the present study. It is, however, conceivable that attenuation of the postprandial glucose response would be reflected in a lower insulin response as well.

Great care was taken to ensure that equal quantities of available carbohydrates were ingested in the test meals. However, there were different CHO sources in the different breads. The design of this study is not appropriate to evaluate the different effects of each particular ingredient, and this represents a limitation of this study.

In affluent countries, a major part of the day is spent in the postprandial phase in which people have their highest blood glucose levels. Hence, it is of special interest to focus upon strategies to reduce high postmeal blood glucose levels. In the present work we have demonstrated appreciable beneficial effects of increasing the pea fibre content in bread. Regular use of pea fibre-enriched bread could be beneficial for attenuating high postprandial excursions of blood glucose, thereby possibly being beneficial for subjects with reduced glucose tolerance. Regular use of pea fibre-enriched bread could be beneficial for weight reduction due to high satiety ratings in combination with attenuated blood glucose levels and lower caloric content if people eat the same amount of bread. Further studies are, however, required to elucidate whether this diet alteration might also serve to prevent type 2 diabetes and cardiovascular diseases.

We emphasize that this study did not aim at comparing the effects of different kinds of fibre. Studies on long-term effects on other coronary risk factors of replacing traditional bread with pea fibre-enriched ones are currently in progress.

## 5. Conclusions

Breads containing a great percentage of pea fibre seem to blunt the rise in blood glucose while still keeping the satiety at a high level, but the apparent effects might partially be attributed to other components. No effect seems to be obtained by increasing the content of rapeseed oil in the pea fibre-enriched bread.

## Conflict of Interests

Idun Industrier (Norway) provided bread and funding to carry through the publication of this paper, including the article-processing charge.

## Acknowledgment

The authors gratefully thank Eva Kristensen and Monica Morris for their excellent technical assistance.

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**Title page:**

**Adjusting the amount and type of carbohydrate in a meal strongly reduced the postprandial glycemic response in Pakistani immigrant women.**

**Running title:**

**“Modification of postprandial blood glucose responses”**

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**Source of support:** Idun Industrier (Norway)  
The Research Council of Norway

**Word count:** 3855

**Trial registration number:** NCT00425269

**Key-words:** postprandial blood glucose levels, cornflakes, chickpeas, Pakistani immigrant women, diabetes prevention.

**Category:** original articles

## Abstract

**Background:** Ethnic minorities living in developed countries have a high prevalence of Type 2 Diabetes (T2D).

**Methods:** Applying a cross-over design, blood glucose was determined every 15 min after intake of various types and amounts of food; cornflakes with milk, chick peas with tomato and onion or bread, in twenty female Pakistani immigrants living in Norway.

**Results:** Sustained elevated postprandial glycemia (PPG) was found after intake of cornflakes providing 75g available carbohydrates (CHO). Intake of cornflake giving 25g CHO reduced the blood glucose peak value (PV) by 11% ( $p=0.008$ ) and Incremental Area Under the 2-h blood glucose vs. time Curve (IAUC) by 51% ( $p=0.003$ ). IAUC was reduced by 40% ( $p=0.001$ ) when lowering bread intake by 50%. PPG was also lowered after intake of 50g CHO as chick peas spiced with tomato and onion, compared with the same amount of available CHO as corn flakes with milk. Change to chick pea type of CHO resulted in a reduction in PV (15.7%,  $p=0.0001$ ), and IAUC (50.9%,  $p=0.0001$ ), and increased the time to reach PV, on average by 20 min ( $p=0.006$ ), and the glycaemic profile by 73.5%  $p=0.002$ . The order of post meal blood PV to one CHO type (amount) corresponded well with the response order to another CHO type (amount) ( $r>0.9$ ,  $p<0.001$ ).

**Conclusion:** In diabetes prone subjects the PPG can be appreciably blunted both by reducing the quantity and changing the quality of the ingested carbohydrates. Below the diabetes threshold there seems to be high- and low responders to a carbohydrate load.

## INTRODUCTION

The prevalence of Type 2 Diabetes (T2D) is increasing globally and poses major public health challenges (1). Ethnic minorities living in developed countries usually exhibit a greater risk of developing T2D. They acquire diabetes at an earlier age, accompanied by higher morbidity and mortality rates (2,3). In Norway, especially immigrants from Pakistan have a high prevalence of T2D (4-6). The prevalence of T2D was found to be 12% among female Pakistani immigrants in the InnvaDiab study (5) while the prevalence of T2D in the host population (including immigrants) in age group  $\geq 30$  years is estimated to be 3.3% (female) and 3.6% (men)(7).

Diabetes is characterized by an elevated blood glucose concentration, and the highest concentrations are encountered in the first hours after intake of carbohydrates. It is well known that the magnitude and duration of the postprandial blood glucose (PPG) elevation are important risk factors for diabetes and coronary heart diseases (8). Indeed, mal regulation of the postprandial glucose elevations is an independent risk factor for several lifestyle diseases (9,10).

It seems accordingly important to attenuate the post meal excursions of blood glucose, especially in diabetes prone subjects, such as the Pakistani immigrants. This raises the question of how such blood glucose regulation could be brought about. Among factors governing PPG are light postmeal walking (11), reduced stress (12), and modifying the amount and type of ingested carbohydrates (13-15). In the present work we have focused upon the acute effects of the type and amount of carbohydrate in meals. It seems that there may also be ethnic differences in the glycemic response to carbohydrates. Thus, Dickinson et al (16) found that the postprandial hyperglycemia and insulin sensitivity varied among

different ethnic groups, and that lean, young South East Asians had the highest postprandial glycemia and the lowest insulin sensitivity in response to a realistic carbohydrate load.

To our knowledge, the question of how PPG will respond to moderate changes in the amount and type of carbohydrates in the meal seems to be poorly investigated in diabetes prone subjects, such as Pakistani immigrants.

A previous study suggested that there are high and low responders to a glucose load, and that high responders might have a special benefit of using low glycemic foods (17).

Thus, in diabetes prone Pakistani immigrant women, the aim of the present work was to investigate to what extent 1) moderate adjustments of the amount and type of ingested carbohydrates would influence PPG, and 2) the glycemic response one day is correlated with the response another day.

## **METHODS**

### *Ethics*

The study was carried out according to the Helsinki declaration and was approved by The National Committees for Research Ethics, Norway, 2.2008.2456. All participants have given an informed written consent for their participation.

### *Subjects*

For this study we recruited 20 female Pakistani immigrants living in Oslo. The participants had completed the InnvaDiab study. This ethnic group has a high prevalence of blood glucose disturbances (5). The 20 participants were randomly allocated into two groups. Group I consisted of 10 subjects who participated in four experiments, in a cross-over design, where

the blood glucose concentration was measured after intake of either cornflakes with milk providing 25g, 50g or 75g CHO, or chick peas with tomato and onion providing 50g CHO; the meals were given on separate days, 7 days between each experiment. Group II consisted of 10 subjects who one day ingested an amount of bread providing 25g CHO, and another day, an amount providing 50g CHO of the same bread. Baseline data for the participating subjects are presented in Table 1. Four participants in group I and 3 participants in group II had an impaired oral glucose tolerance test (OGTT) with blood glucose concentration above 7.8 mmol/L 2 h after glucose ingestion. All participants had waist circumference  $\geq 80$  cm. No subjects used glucose lowering medication.

Cornflakes and bread were chosen since they represent common high GI food items in Norway, and chick peas because this is a low glycemic food item regularly used by Pakistani immigrants. Thus, by using these foods we would also have results to compare PPG after a typical Pakistani food item (chickpeas) and a “Western-type food” (cornflakes).

The meal sizes were chosen to be in the range used by many people; e.g. two thin slices of bread would provide about 25 g CHO. Even an intake of 75 g CHO in a meal, for example 4-5 slices of bread, is not unusual. Additionally, 75 g CHO is the amount given in the regular OGTT. Therefore, these doses represent realistic carbohydrate intake in meals, and at the same time would provide dose response data.

#### *Experimental setup*

In this study we applied a randomized crossover design. On separate days and after an overnight fast, the subjects arrived at 0845 and sat resting until 0900. At that point, the fasting blood glucose concentration was measured in triplicate i.e. 3 measurements were carried out

on 3 consecutive drops of blood, from the same finger stick, and subsequently one test meal was served. The post meal blood glucose concentration was measured every 15 min during a 2-h period after the start of the test meal while the participants sat round a table and had the opportunity to speak freely in their own language.

### *The meals*

Group I was served three different portion sizes of Cornflakes (Kellogs Ltd.) (84.0g available CHO and 3.0g fibre/100g) with semi skimmed milk (Tine Meierier, Norway) (4.7g available CHO/100g). The amount of milk was kept constant at 2 dl per portion but the amount of cornflakes was calculated to obtain 25g, 50g or 75g of available CHO, from cornflakes with milk, per portion respectively. In addition, group I was served a meal consisting of canned chick peas (Viter, Spain) (19.6g available CHO and 5.4g fibre/100g) flavoured by some small tomato pieces (3.3g available CHO and 1.3g fibre/100g) and onion pieces (9.1g available CHO and 2.1g fibre/100g) prepared to include 50g available CHO. The experiments were performed on separate mornings with one week between subsequent sessions.

Group II subjects were served sliced bread (Idun Industrier, Norway) (40.1g available CHO and 4.6g fibre/100g), if preferred toasted, with 2 dl of tap water. The portion sizes of bread were calculated so as to obtain 25g or 50g available CHO, respectively. The experiments were performed on separate mornings with three weeks between subsequent sessions.

Data for available carbohydrate and dietary fibre, was provided by the manufacturers.

Macronutrient and fiber composition of each meal is given in table 2.

### *Anthropometric and blood measurement data*

Data for age, weight, height, waist circumference, blood pressure, HbA<sub>1c</sub> and OGTT were collected on a separate day as part of the follow-up in the InnvaDiab study (5) in which the subjects had participated.

#### *Pre- and postprandial blood sampling and blood glucose measurements*

Capillary blood glucose concentrations (mmol/L) were measured (Ascensia Contour, Bayer) before the meal and again at 15, 30, 45, 60, 75, 90, 105 and 120 min in the postprandial phase. As informed by the manufacturer, the glucometers from Bayer had a total error (system plus user error) of  $\leq 10\%$  thus providing clinically and analytically acceptable results (18) (19). We nevertheless have re-examined the variability. Using the same blood sample we determined the glucose concentration 10 times consequentially on each of 14 different Ascensia Contour apparatuses. After this test, we chose the three most accurate ones, which had intra assay coefficients of variation ranging from 2.2 to 2.3%.

The average blood glucose value of the three pre meal measurements was used as the basal value in the statistical calculations.

#### *Statistical methods*

The primary outcome of this study was the overall postprandial glycemia, as estimated by several measures:

PV= postprandial blood glucose peak value

TTP= time to reach PV from zero time

IPV= incremental PV, i.e. PV minus the fasting blood glucose concentration

GP= glycemic profile, i.e. the duration of the incremental postprandial blood glucose response divided with the blood glucose incremental peak value

IAUC= the Incremental Area Under the glucose vs. time Curve, calculated by the linear trapezoidal rule (WHO 1997) (20).

Data were analyzed using SPSS 15.0. All data were assessed for normal distributions.

Comparison of mean values of normally distributed data within groups were performed by paired samples Student's t test. For each group, a two-factor within-subject repeated measure ANOVA was used to test the effects of time and intervention, and the interaction between time and intervention. To assess whether there were high- and low responders to a glucose load, we correlated the glycemic responses to intake of various amounts of carbohydrate. Data are reported as mean values  $\pm$  SEM in figures, or mean with SD in text and tables.

## RESULTS

### **Postprandial blood glucose responses to different portion sizes of the same food.**

#### ***Cornflakes with milk (Figure 1, left panel)***

The glycaemic response after ingestion of cornflakes with milk was equivalent for all portion sizes until 30 min. At this point the average blood glucose leveled off for the smallest portion but continued to increase for the other two portion sizes. The average blood glucose dropped gradually from 45 min and throughout the 2h period whereas only the smallest portion allowed the blood glucose level to return to fasting values within 2h. However, the blood glucose concentration obtained after ingestion of 75g CHO stabilized above 8.5 mmol/L, after reaching the peak value at 45 min, and remained at a high level throughout the 2h test period. A significant difference was found in several glycaemic measures when comparing the smallest with the largest portion of Cornflakes with milk; PV ( $p=0.008$ ), TTP ( $p=0.005$ ), IPV ( $p=0.004$ ) and IAUC ( $p=0.003$ ). We found no significant group differences in GP. (Table 3)



Using repeated measures ANOVA we found a significant main effect of time and portion size ( $F= 12.2$  and  $16.1$  respectively,  $p\text{-value} < 0.005$ ) and an interaction between time and portion size ( $p<0.005$ ).

***Bread (Figure 1, right panel)***

After intake of 50g CHO the blood glucose concentration increased during the first 45 to 60 min, and then leveled off until 75 min. Then the concentration decreased slowly, but was still elevated after 120 min. After ingestion of 25g CHO approximately the same peak value was reached, but the curve decreased more rapidly than after ingesting 50g CHO so that the baseline level was reached after 120 min. There were significant differences between the blood glucose values at each time point from 60 min and throughout the observation period ( $p < 0.05$  for all time points), and a significant reduction in IAUC ( $p = 0.001$ ). We found no significant changes in other measures of the glycemic responses, i.e. in PV, TP, IPV or GP after ingesting 25g instead of 50g CHO (Table 3).

Using repeated measures ANOVA we found a significant main effect of time and portion size ( $F= 37.4$  and  $27.3$  respectively,  $p\text{-value} < 0.001$ ) and an interaction between time and portion size ( $p<0.001$ ).

**Postprandial blood glucose responses to different *types* of CHO.**

***A comparison of the PPG effect of 50g CHO in either cornflakes or chick peas.***

As shown in Figure 2, there was a rapid increase in blood glucose during the first 30 min after intake of 50g CHO as Cornflakes with milk. The average blood glucose continued to increase until 45 min and then decreased steadily until 105 min. Blood glucose values was still above

baseline value after 2h. In contrast, after intake of the same amount of available CHO as chic peas, a slow increase in blood glucose was observed during the first 45 min but the peak value was significantly lower ( $p=0.0001$ ) and significantly sustained ( $p=0.006$ ) than after intake of 50g CHO as cornflakes. The average blood glucose value returned to baseline level after 2h. A significant change in all glycaemic measures was obtained when comparing the same available CHO from cornflakes vs chic peas PV ( $p=0.0001$ ), TTP ( $p=0.006$ ), IPV ( $p=0.0001$ ) GP ( $p=0.002$ ) and IAUC ( $p=0.001$ ).

Using repeated measures ANOVA we found a significant main effect of time and CHO type ( $F= 10.0$  and  $30.5$  respectively,  $p < 0.05$ ) and an interaction between time and CHO type ( $p < 0.05$ ).

### **Is there a correlation between the glycemic response to intake of various amounts of cornflakes and chic peas?**

The relationship between blood glucose PV after ingestion of various amounts of cornflakes or chic pea meals was investigated using Pearson product-moment correlation coefficient.

There was a strong positive correlation ( $r=0.917$ ,  $r=0.948$ ,  $r=0.880$ ,  $r=0.943$ ,  $r=0.903$ ,  $r=0.919$ ) between PV after intake of the different cornflake meals and a chic pea meals; all with  $p\text{-values} \leq 0.001$ . This means that subjects responding with a high (low) blood glucose PV after cornflake or chic pea intake one day also responded with a high (low) value another day. Two of the correlations are shown in figure 3; i.e. between two portions sizes of cornflakes, and between cornflakes and chic peas.

## **DISCUSSION**

The present study in T2D prone women suggests that the postprandial glucose elevations after carbohydrate intake can be appreciably blunted both by reducing the quantity and changing the quality of the ingested carbohydrates. Thus, consideration of type and amount of ingested carbohydrates would seem of crucial importance to govern the postprandial blood glucose concentration in this group.

Despite having knowledge about the importance of good glucose control to prevent T2D and to avoid complications after the onset of the disease, many immigrants have difficulty in regulating blood sugar levels in a satisfactory manner. It is therefore desirable to find cost-effective ways to communicate how the blood glucose levels are affected by food intake, physical activity and stress/coping.

Extended duration of elevated blood glucose levels has previously been recognised as an independent risk factor diabetic complications and CVD (9). The present study shows that, in diabetes prone subjects, the blood glucose elevation the first 15 min after intake of carbohydrates can be the same for various portion sizes. However, the glycemic response to a moderate carbohydrate intake seems to continue to increase for another 15 min. Indeed, after a high carbohydrate intake the level of blood glucose in this group of subjects may remain at the peak level for at least two hours. Accordingly, diabetes prone subjects should be especially aware of the strong glycemic impact of eating different amounts and types of carbohydrates.

Unfortunately, we did not measure insulin in this study. Nevertheless, the prolonged high levels of glucose measured after the greatest portion of cornflakes make it probable that these subjects may have high levels of insulin, as an indication of reduced insulin sensitivity, but we have no data to confirm this suggestion. Among the several effects of this hormone (21)

are inhibition of adipose tissue lipolysis and fat oxidation, enhanced formation of fatty acids and triglycerides, thereby promoting fat deposition and overweight. Furthermore, insulin stimulates triglyceride and VLDL synthesis in the liver with ensuing dyslipidemia. Thus, hyperinsulinemia following prolonged post meal hyperglycemia may be a contributing factor for the high prevalence of obesity found in these women.

The International Diabetes Federation (IDF) recommends that patients with diabetes manage their blood glucose levels by addressing both fasting blood glucose and post meal glucose (PPG). The guidelines recommend that PPG levels should not exceed 7.8 mmol/L during the 2 hours post meal period (8). As indicated in our study, this goal seems to be obtained either by using low glycemic carbohydrates, such as chickpeas (22) or by reducing the CHO intake in each meal.

In the present study we used two high glycemic foods, i.e. cornflakes and bread, and one low glycemic food (chick peas) (22). A number of factors influence the glycemic response to food (23), but most important is the type and amount of carbohydrate (24). The meals served in the current study differed in macronutrient composition. One effect of fibre is to delay gastric emptying, thereby slowing digestion, and reducing the postprandial excursions of both glucose and triglycerides (25). Also fat has been found to delay gastric emptying (26). Furthermore, amino acids may stimulate both insulin and glucose-dependent insulinotropic polypeptide (GIP)(27). Milk protein in particular, appears to stimulate an increase in postprandial insulin response with corresponding reductions in postprandial blood glucose levels (28,29). It would appear, therefore, that co-ingestion of the non-carbohydrate nutrients of the diets used in our study might have modified the observed blood glucose excursions after the meals.

The sample size of the study was small. However, the cross over design of the study would reduce the measurement variability and the number of subjects is in line with the recommendations for glycaemic index testing (30,31). Nevertheless, the low number of participants is a limitation concerning external validity.

For the healthy part of the population the total amount of carbohydrate probably should not be altered much. However, if low PPG responses are considered beneficial, one way to obtain this effect could be to use low glycemic diets, e.g. those tested in the present study. Especially for diabetes prone subjects, such as the participants of the present study, it would seem reasonable to reduce the glycemic load, e.g. by using CHO with low glycemic effects. Furthermore, if high glycemic foods are used (such as cornflakes) it would seem appropriate to recommend reduction in the amounts ingested per meal. However, the present study was not designed to evaluate the optimal macronutrient composition of meals.

Most of the modern starchy foods, such as breads and cornflakes have relatively high GI, and are consumed in high amounts, implying high glycemic load ( $GL=GI \times \text{amount CHO}$ ) (32). In the present study we did not measure GI of the foods used, since, the concepts of GI and GL do not include information about the course of the postprandial blood glucose curve. Several studies have suggested that the blood glucose fluctuations are associated with oxidative stress and inflammation (33). Therefore, we rather use the term glycemic response, with reference to the 2 h post meal blood glucose curves. Previously, the glycemic profile (GP) has been defined as the duration of the incremental postprandial blood glucose response divided by the blood glucose incremental peak value (min/mM) (34).

There seems to be a wide variability between subjects in the glycemic responses to particular foods(17). By definition, a subject is diagnosed as diabetic when repeatedly found to exceed diabetic limits for fasting blood glucose. In the present work we tried to explore if a subject, in spite of having a normal fasting blood glucose concentration (FBG), could still be characterized as a high CHO responder, and conversely, whether a low responder to one type and amount of CHO would also be a low responder to other types and amounts of CHO. The present results suggest so. Thus, even with normal FBG, there seems to be subjects who may be characterized as high responders to CHO intake. The observation raises the question of whether they in the course of time will develop diabetes, but we have no data to substantiate the hypothesis. An important public health strategy should accordingly be to encourage people to be aware of their own tolerance for carbohydrates, as well as informing about the importance of keeping the blood sugar within a narrow range. Dietary information should be given to enable people to design their diet to limit the post meal glucose excursions. These recommendations are in line with recommendations from an Asian-Pacific expert panel who encourage increased screening for PPG and address the importance of blood glucose management in the postprandial period (35). Fasting plasma glucose and HbA<sub>1c</sub> are the most commonly measured glycemic variables. However, these variables do not seem to completely reflect the glycemic control, which probably could more appropriately be assessed by the incremental area under the glucose vs. time curve (IAUC). A standardized IAUC measurement of postprandial glucose requires however an oral glucose tolerance tests (OGTT), which unfortunately seems unrealistic to carry out on a population basis. In our experience, repeated measurements of the blood glucose concentration, for example one hour after a common carbohydrate meal may be easier to perform.

The incremental area under the glucose vs. time curve (IAUC) is probably an appropriate indicator of the glycation potential, which presumably could be blunted by using smaller portion sizes of high glycemic carbohydrates, or changing to low glycemic foods.

It has previously been claimed that immediate visual feedback (visual bio-feedback) upon their own biological responses, for example the blood glucose elevation after carbohydrate intake can strongly aid to enhance the understanding and motivation for change (36). We suggest that the observed changes in blood glucose curves following moderate diet adjustments could serve in this regard. However, although the participants were shown their own blood glucose curves, and reported increased motivation for dietary change, the present study was not designed to assess this theory of learning. Blood glucose measurements with handheld meters is easy to implement in practice and meets the requirements for speed and accuracy required in order to provide rapid feedback on changes in blood glucose levels.

An important public health strategy could be to increase the number of available processed carbohydrate-rich foods with a lower glycemic potential than their regular counterparts. We recently published data that would seem in support of the general hypothesis that inclusion of fibre is beneficial for improved blood glucose control in female Pakistani immigrants (37).

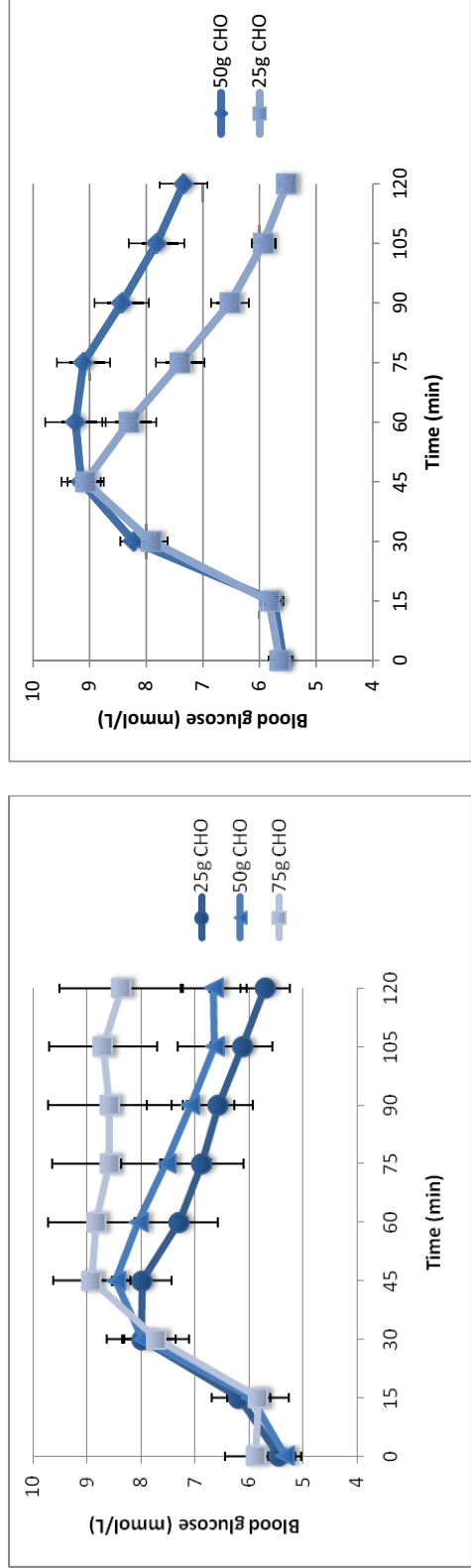
In conclusion, in diabetes prone subjects the postprandial glucose elevations after carbohydrate intake can be appreciably blunted both by reducing the quantity and changing the quality of the ingested carbohydrates. Consideration of type and amount of ingested carbohydrates would seem of crucial importance to govern the postprandial blood glucose concentration in this group.

## **Acknowledgements**

The technical assistance of Eva Kristensen and Monica Morris is gratefully acknowledged.

Idun Industrier (Norway) provided bread, and also funding for one of the authors.

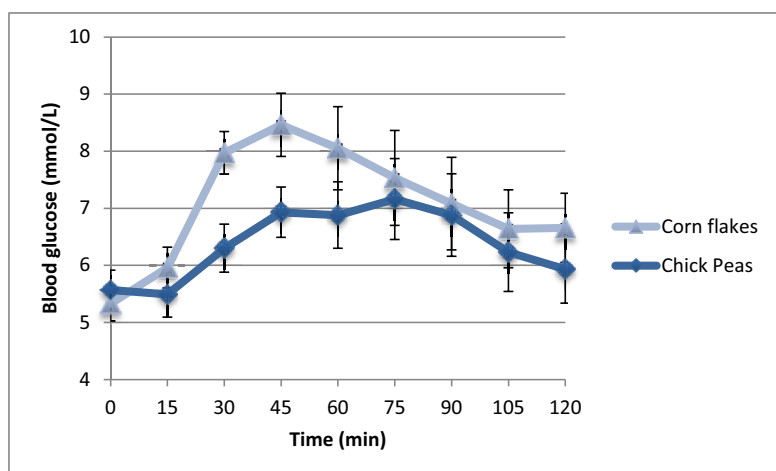




**Figure 1. Blood glucose concentration after intake of different portion sizes of *high glycemic* meals, i.e. cornflakes with milk (left panel) and bread (right panel).**

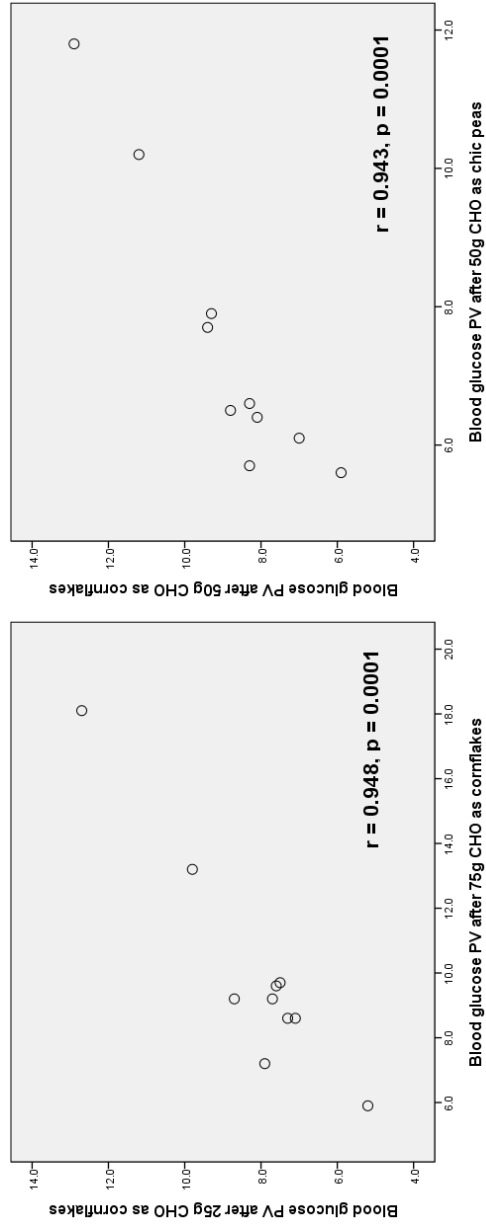
*Left panel:* On separate days and after an overnight fast, the blood glucose concentration was determined after ingestion of three portion sizes of cornflakes with milk (n=10). Total amount of available carbohydrates (CHO) was 25g (closed circles), 50g (closed triangles) and 75g (closed squares). **Mean values  $\pm$  SEM.** Note broken y-axis. Corresponding blood glucose values after ingestion of 25g or 50g CHO were significantly different; for postprandial blood glucose peak value (PV) (p=0.015), for incremental peak value (IPV) (p=0.042), for the Incremental Area Under the 120 min glucose concentration vs. time Curve (IAUC) (p=0.026). Corresponding values after ingestion of 25g or 75g CHO differed significantly for PV (p=0.008), time to peak value (TTP) (p=0.005), IPV (p=0.004) and IAUC (p=0.003). Comparing 50g and 75g CHO: significant difference for TTP (p=0.004) (n=10).

*Right panel:* On separate days and after an overnight fast, the blood glucose concentration was determined after ingestion of two portion sizes of regular coarse bread (n=10). Total amount of available CHO was 50g (closed diamonds) and 25g (closed squares). **Mean values  $\pm$  SEM.** Note broken y-axis. There were significant differences between the blood glucose values at each time point from 60 min and throughout the observation period ( $p < 0.05$  for all time points), and a significant difference in IAUC ( $p=0.001$ ) (n=10).



**Figure 2. Blood glucose concentrations after intake of a high and a low glycemic meal.**

On separate days and after an overnight fast, the blood glucose concentration was determined after ingestion of 50g available CHO either as cornflakes with milk (closed triangles), or Chick Peas with tomato and onion (closed diamonds). **Mean values  $\pm$  SEM.** Note broken y-axis. There were significant differences for corresponding values of postprandial blood glucose peak value (PV) ( $p=0.001$ ), time to peak value (TTP) ( $p=0.006$ ), incremental peak value (IPV) ( $p=0.0001$ ), glycemic profile (GP) ( $p=0.002$ ), and Incremental Area Under the 120 min glucose concentration vs. time Curve (IAUC) ( $p=0.001$ ) ( $n=10$ ).



**Figure 3: Correlation between the peak blood glucose value (PV) after intake of two amounts of cornflakes (left panel) and after intake of cornflakes or chic peas (right panel).**

There was a significant positive correlation between the blood glucose PV after ingestion of 25g or 75g available CHO as cornflakes with milk,  $r=0.948$ ,  $p=0.0001$  (Pearson product-moment correlation coefficient), and between blood glucose PV after ingestion of 50g available CHO either as cornflakes with milk or as chic peas spiced with tomato and onion,  $r=0.943$ ,  $p=0.0001$  (Pearson product-moment correlation coefficient) ( $n=10$ ). Angi p-verdi  $p<0.001$ , istedenfor en ti-tusen-del?

**Table 1. Baseline characteristics of the participants.**

Test groups	Group I (n=10)		Group II (n=10)	
	Mean	SD	Mean	SD
Age (years)	44.9	7.50	45.3	8.0
BMI (kg/m <sup>2</sup> )	31.6	5.6	31.0	5.3
Waist circumference (cm)	103.5	11.7	97.0	12.2
Blood pressure (systolic/diastolic)(mmHg)	119/85 <sup>a</sup>	12/9	120/81 <sup>b</sup>	18/11
HbA1c (%)	5.7	0.8	5.6	0.5
Fasting blood glucose (mmol/L)*	5.6	1.2	5.6	0.5
Fasting blood glucose (mmol/L) (OGTT) **	5.6	1.0	5.6	0.2
2-h blood glucose value (mmol/L) (OGTT) **	9.2	2.8	8.6	1.8

a) Average of measurements on the four experimental days.

b) Measured as part of the InnvaDiab study

\* Average baseline value all experimental days.

\*\* Value obtained in a standardized Oral Glucose Tolerance Test (OGTT).

Table 2: Macronutrient and fiber content of meals

Macronutrient and fiber content (g/meal)					
Group	Test food	CHO*	Fibre	Protein	Fat
I (n=10)	Cornflakes with milk**	25	0.6	6.8	4.3
	Cornflakes with milk	50	1.5	7.0	6.4
	Cornflakes with milk	75	2.3	7.3	8.5
	Chick peas, tomato and onion	50	14	13	2.0
II (n=10)	Regular bread	25	2.8	5.3	1.7
	Regular Bread	50	5.7	10.7	3.4

\*Available CHO; \*\* Semi skimmed with fat 1.5%, protein 3.3% and CHO 4.7%.

Table 3. Various measures of the glycemic response after ingestion of various foods (mean ± SD).

Test groups	Group I			Group II		
Interventions	Cornflakes with milk			Chic Peas with onion and tomato	Bread	Bread
Amount of CHO (g)	25	50	75	50	25	50
PV (mmol/L)	8.2 ± 2.0	8.9 ± 2.0	9.9 ± 3.4	7.5 ± 2.0	9.8 ± 0.4	9.2 ± 0.4
TTP (min)	36 ± 10	48 ± 15	74 ± 29	68 ± 18	55 ± 5	47 ± 4
IPV (mmol/L)	2.7 ± 1.2	3.6 ± 1.5	4.1 ± 1.8	1.9 ± 1.1	4.2 ± 1.2	3.6 ± 1.1
GP (min* L* mmol <sup>-1</sup> )	38.4 ± 30.4	39.6 ± 34.3	38.0 ± 26.5	68.7 ± 51.7	30.3 ± 8.7	28.9 ± 9.2
IAUC (mmol * L <sup>-1</sup> * min)	129 ± 114	226 ± 127	261 ± 116	111 ± 83	295 ± 26	178 ± 23

PV= postprandial blood glucose peak value; TTP=, time to peak value, IPV=incremental peak value; GP=glycemic profile; IAUC= Incremental Area Under the 120 min glucose concentration vs. time Curve.

- Comparison of different *portions* of cornflakes:
  - 25g CHO vs. 50g CHO, PV (p=0.015), IPV (p=0.042) and IAUC (p=0.026). For TTP and GP (NS).
  - 25g CHO vs 75g CHO, PV (p=0.008), TTP (p=0.005), IPV (p=0.004) and IAUC (p=0.003). For GP (NS).
  - 50g CHO vs 75g CHO, TTP (p=0.004). For PV, IPV, GP and IAUC (NS).
- Comparison of 50g CHO in cornflakes and 50g CHO in chic peas: PV (p=0.0001), TTP (p=0.006), IPV (p=0.0001), GP (p=0.002) and IAUC (p=0.0001).
- Comparison of different portions of bread: IAUC (p=0.001) For PV, TTP, IPV and GP (NS).

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## **Slow postmeal walking reduces the blood glucose response– an exploratory study in female Pakistani immigrants**

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## ABSTRACT

**Background:** Postprandial physical activity may blunt the blood glucose response. In diabetes prone female immigrants only slow walking is regularly performed raising the question of whether also this type of physical activity can attenuate their post meal blood glucose elevation.

**Methods:** Using a cross over design, 11 female Pakistani immigrants living in Oslo were recruited to participated in three experiments where their blood glucose concentration was measured every 15 min for 2h after intake of a high glycemic food, either while resting after the meal or doing very light post meal walking of two durations.

**Results and discussion:** Postprandial blood glucose peak value (PV) and Incremental Area Under the 2h blood glucose Curve (IAUC) decreased with increasing duration of slow post meal walking. Also the blood pressure was lowered.

**Conclusion:** Post meal walking can strongly attenuate the glycemic response to carbohydrates and reduce blood pressure in a high risk group of immigrants.

Trial registration number: NCT00425269

Key –words; postprandial glucose levels, cornflakes, light physical activity, immigrants

## INTRODUCTION

Pakistanis, constituting one of the largest immigrant groups in Norway are especially prone to develop obesity and type 2 diabetes (T2D), and women are more liable than men (1;2).

Epidemiological data strongly suggest that increased physical activity is a positive factor in the prevention of T2D and the metabolic syndrome (MetS), which may lead to T2D.

Conversely, studies of varying design support the hypothesis that a sedentary lifestyle may promote the development of MetS and T2D (3). It would appear, therefore, that increased physical activity should be especially recommended for diabetes prone subjects, such as Pakistani immigrants. The present study investigated one particular aspect of how physical activity might influence the blood glucose concentration.

An early sign of developing diabetes is an increasingly poorer postprandial glycemic control after intake of carbohydrates. Indeed, mal regulation of the postprandial glucose elevation after a carbohydrate rich meal seems to be an independent risk factor for several lifestyle diseases (4-6).

Data from observational and randomised trials suggest that approximately 30 minutes of moderate intensity physical activity, such as walking, at least 5 days per week may substantially reduce the risk of developing T2D (3). In line with this, Norwegian health authorities recommend minimum 30 min of physical activity per day at an intensity of 12-13 on the Borg's scale (7) (8).

Pakistani immigrants living in Norway do not engage much in various sport activities (9).

However, as shown by Hjellset et al., (9) Pakistani immigrant women practise low intensity

walking regularly. In fact, by accelerometer recordings it was recently observed that number of steps are close to 10 000 per day, which is approximately according to the recommended level (8).

Earlier studies in healthy ethnic Norwegians offer a background for exploring to what extent slow walking may improve the glycemic control in this group of diabetes prone subjects. Thus, Høstmark et. al. showed, in 2006, that the postprandial glucose concentration can be appreciably attenuated by light post meal physical activity, as observed both in healthy young and middle-aged, sedentary and trained women (10). These findings were subsequently extended to include also lower intensity post meal physical activity, i.e. bicycle exercise at 59 to 67 % of  $HR_{max}$  (11), and post meal walking. Indeed, the magnitude of the blood glucose blunting effect of walking after a meal was comparable to that of the alpha glucosidase inhibitor acarbose (12).

The above data in healthy Norwegians prompted us to do an exploratory study to see whether even the very low intensity physical activity habitually carried out by a group of diabetes prone Pakistani immigrant women living in Oslo, could also blunt their blood glucose elevation after carbohydrate intake, if such activity was carried out in the immediate postprandial period.

The aim of the present work was accordingly to observe whether slow post meal walking would attenuate the blood glucose response to carbohydrate intake in a small group of diabetes prone Pakistani immigrant women living in Oslo, Norway. Since light physical activity, such as walking, may reduce blood pressure (13) we also included determination of blood pressure before and after light post meal walking.



## METHODS

### *Ethics*

The study was carried out according to the Helsinki declaration and was approved by the The National Committees for Research Ethics, Norway, 2.2008.2456. All participants have given an informed written consent for their participation.

### *Subjects*

For this study we recruited 11 female Pakistani immigrants living in Oslo, Norway. The participants were randomly selected among the subjects who had been partaking in the InnvaDiab study (14). i.e. female immigrants, 25 years or older, and with both parents of Pakistani origin. Baseline data for the participating subjects are presented in Table 1. Mean age of the participants was 44 years (range: 30 to 56), and mean body mass index (BMI;  $\text{kg/m}^2$ ) 30.9 (range: 24.6 to 45.9). The average glycated hemoglobin ( $\text{HbA}_{1c}$ ) value was 5.5 % (range: 5.0 to 6.1). Fasting blood glucose measured on the three experimental days was 5.5 (range: 4.4 to 7.2). Five participants had an impaired oral glucose tolerance test (OGTT) with fasting blood glucose concentration above 7.8 mmol/L (2 subjects) or blood glucose above 11.1 mmol/L (3 subjects) 2h after ingestion of 75g glucose. All participants had waist circumference  $\geq 80$  cm. Subjects on glucose lowering medication were excluded from the study.

### *Experimental design*

A cross-over design was applied to study the effect of post meal walking. On separate days and after an overnight fast, 11 subjects participated in three experiments, in a crossover

design. One of the days the subjects rested after ingesting a carbohydrate meal (see below). One week later the same subjects walked for 20 min after the same meal, and one more week later, all subjects walked for 40 min after the meal. Thus, all the subjects participated in the same experiment (same walking duration) on each experimental day. However, one of the subjects did not participate in the 40 min postmeal walk. The participants were asked to behave as similarly as possible on the day before the experiments, and to fast for 12 hours before the experiments. Anticipating that there possibly could be variation in diet and physical activity on different days of the week, for each subject we chose to do all the experiments on the same day of the week.

On experimental days, the subjects arrived at 0845 and sat resting until 0900. At that point, the fasting blood glucose concentration was measured in triplicate, and subsequently a test meal consisting of corn flakes with milk, providing 50 g available carbohydrates (CHO), was served. The subjects consumed the meal in a comfortable place within 15 min. The post meal blood glucose concentration was measured repeatedly during a 2h period after the start of the test meal. The participants sat resting after the walk and throughout the 2h observation period. Pakistani immigrant women regularly practice slow walking. Therefore, this type of physical activity was used in the studies. The participants were encouraged to use their habitual walk with small steps without changing clothes or shoes. All communication with the participants went through a Punjabi/Urdu speaking research assistant. The participants were allowed to speak freely in their own language during the 2h period.

#### *Anthropometric and blood measurement data*

Data for age, weight, height, waist circumference, HbA<sub>1c</sub> and OGTT were collected on a separate day as part of the InnvaDiab-DEPLAN study (9) in which the subjects had participated.

*Blood sampling and determination of blood glucose and blood pressure measurements*

Capillary blood glucose concentrations (mmol/L) were measured (Ascensia Contour, Bayer) before the meal and at 15, 30, 45, 60, 75, 90, 105 and 120 min in the postprandial phase. As informed by the manufacturer, the glucometers from Bayer had an accuracy of  $\leq 10\%$  thus providing clinically and analytically acceptable results (15) (16). The blood glucose concentration before each meal (time = 0) was measured in triplicate and the average value was used as the basal value in the statistical calculations.

Arterial blood pressure was measured in the sitting position at 0-time and again after 1h and 2h on each experimental day by the use of A&D Medical plus digital blood pressure monitor UA-767 (Tokyo, Japan).

*The slow post meal walks*

The participants were asked to walk in a comfortable slow speed that would mimic an ordinary slow walking situation. No special equipment (shoes or clothes) was required to participate in the experiments. Great care was taken to measure blood glucose levels at the correct intervals during the walks. For that purpose the participants stopped walking for less than 2 min allowing blood glucose measurement.

Subjective perceived exertion in exercise according to Borg (7;17) was recorded on completion of the longest walking session.

### *Calculations*

The primary outcome of this study was the overall postprandial glycemia, as estimated by several measures:

PV= postprandial blood glucose peak value

TTP= time to reach PV from zero time

IAUC= the Incremental Area Under the glucose vs. time Curve, calculated by the linear trapezoidal rule (18;19).

### *Statistics*

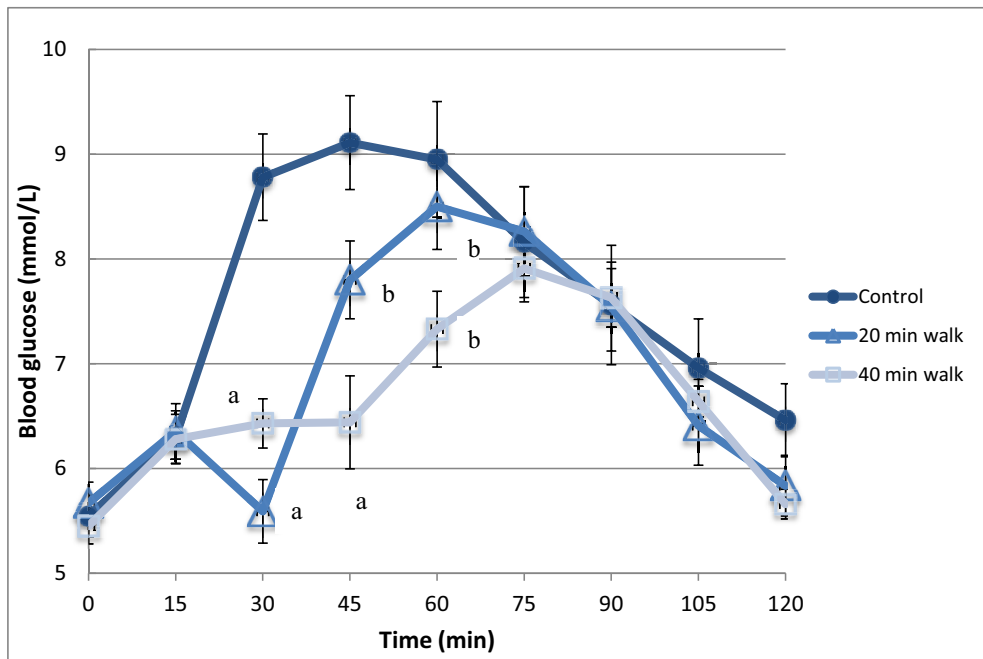
All data were tested for normality and analysed using SPSS for Windows, version 15.0 (SPSS Inc., Chicago, Ill). One-way repeated measures ANOVA was used to determine the main effects of time, and type of intervention, on blood glucose values. Differences between corresponding mean values of PV, TTP and IAUC were assessed using students t-test, paired samples. One woman did not participate in the 40 min postmeal walk. Thus, only 10 subjects could be included in the RM ANOVA analysis.  $P < 0.05$  was considered as statistically significant. Data are presented as means  $\pm$  SEM or SD. We also evaluated the results using the non-parametric Wilcoxon Signed Rank Test, but the outcome did not change.

## RESULTS

*Does post meal slow walking influence the blood glucose responses, and is there an effect of the walking duration?*

When resting after intake of 50 g CHO (n=11), the blood glucose concentration increased during the first 30 to 45 min, reaching a maximum value of 9.1 mmol/L after 45 min. Then the glucose concentration decreased but was still about one mmol/L higher than at baseline at the end of the experiment, i.e. at 2h (figure 1). When **20 min** very slow post meal walking was performed after intake of the same meal the postprandial blood glucose peak value (PV) was lowered by 8.2% (NS), and time to reach the PV was delayed, on average by 19 min ( $p=0.002$ ; paired t-test). These effects of walking were strengthened when the postprandial walk was increased to **40 min**. In this experiment the time to reach PV from zero time (TTP) was delayed by 25 min ( $p=0.001$ ; paired t-test) and the PV was lowered by 16.3% ( $p=0.001$ ; paired t-test). Also non-parametric tests (Wilcoxon signed rank test) provided results comparable to those referred to above: Post meal walking for 20 min vs. resting gave a significant effect ( $p=0.010$ ) to delay TTP, but had no significant effect on PV. In contrast, 40 min walking significantly reduced both PV ( $p=0.005$ ) and delayed TTP ( $p=0.011$ ) as compared with resting. (Figure 1 and table 2). Additionally, after postprandial walking, the blood glucose concentration approached baseline levels after 2h. Using repeated measures ANOVA (n=10) we found a significant main effect of time and duration of light postprandial walk ( $F= 26.8$  and  $6.9$  respectively,  $p < 0.05$ ) and there was an interaction between time after the meal and duration of the walks ( $F= 14.0$   $p<0.001$ ). Thus, time after carbohydrate intake influenced the blood glucose concentration, as well as the type of treatment, i.e. resting after carbohydrate intake, or walking for 20 or 40 min. However, the time course of the glucose curve depended on the type of treatment.

The subjective perceived exertion caused by 40 min walking was reported as “very light” (range 6 to 12, i.e. “extremely light” to “light”), according the Borg’s scale (7), with a mean value of 8 (“very light”).

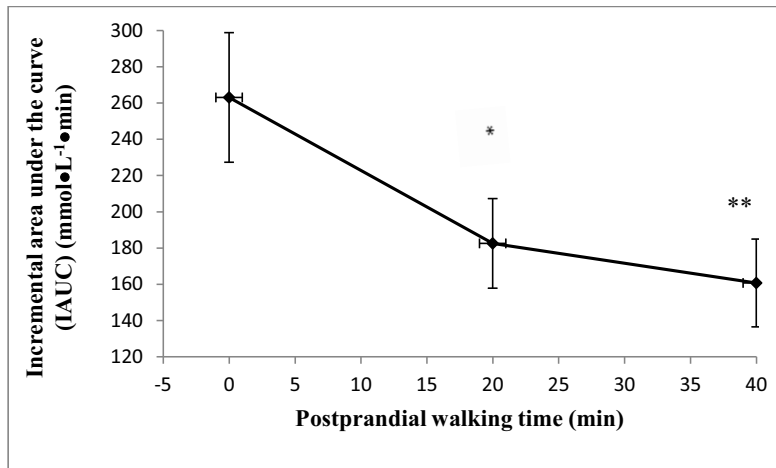


**Figure 1. Blood glucose concentration as influenced by postprandial very light physical activity (walking).** On separate days and after an overnight fast, the blood glucose concentration was determined before (time=0) and after ingestion of corn flakes and milk, providing 50g carbohydrates (meal finished after 15 min) and then every 15 min for 2 hours. The two hour period included a 20 min walk (from 15 to 35 min) (open triangles, n=11) or a 40 min walk (from 15 to 55 min) (open squares, n=10) after the meal. On the control day the

participants sat resting for the entire 2h period (closed circles,  $n=11$ ). **Mean values  $\pm$  SEM.**

Note broken y-axis. <sup>a</sup>  $p < 0.001$  vs. control. <sup>b</sup>  $p < 0.05$  vs. control.

The two-hour incremental area under the blood glucose curve (IAUC) was reduced by 30.6 % after 20 min walk as compared with the control day ( $p=0.025$ ) ( $n=11$ ) (Figure 2) and by 39.0 % after 40 min walk vs. the control day ( $p=0.006$ ) ( $n=10$ ).

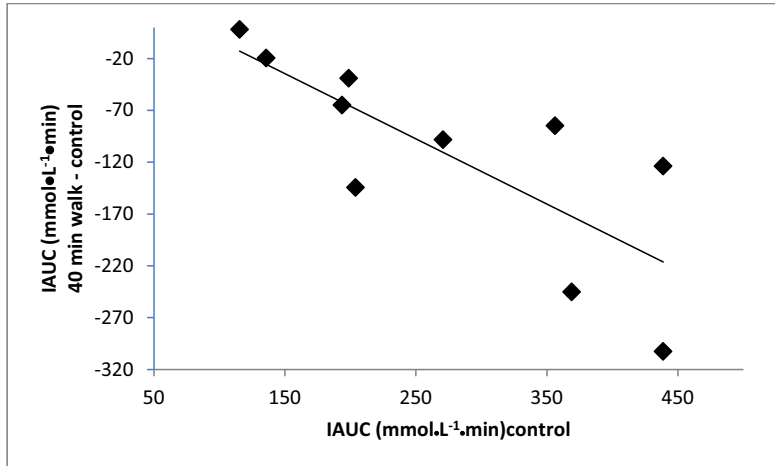


**Figure 2. Two-hour incremental area under the blood glucose curve (IAUC) as related to the postprandial walking time.** \* $p=0.025$  vs. control (i.e. without post meal walking), \*\* $p=0.006$  vs control, **mean value  $\pm$  SEM** 10 subjects participated in the 40 and 20 min post meal walking experiment, respectively.

*Is the reduction in blood glucose by slow post meal walking related to the magnitude of the response without walking?*

Subjects with the largest IAUC on the control day demonstrated the greatest reduction in postprandial glucose response when walking 40 min after the meal (figure 3). There was a

negative correlation between IAUC on the control day and the difference between IAUC control and IAUC 40 min walk, Kendall's Tau, -0.719,  $p=0.004$ ,  $n=10$ .



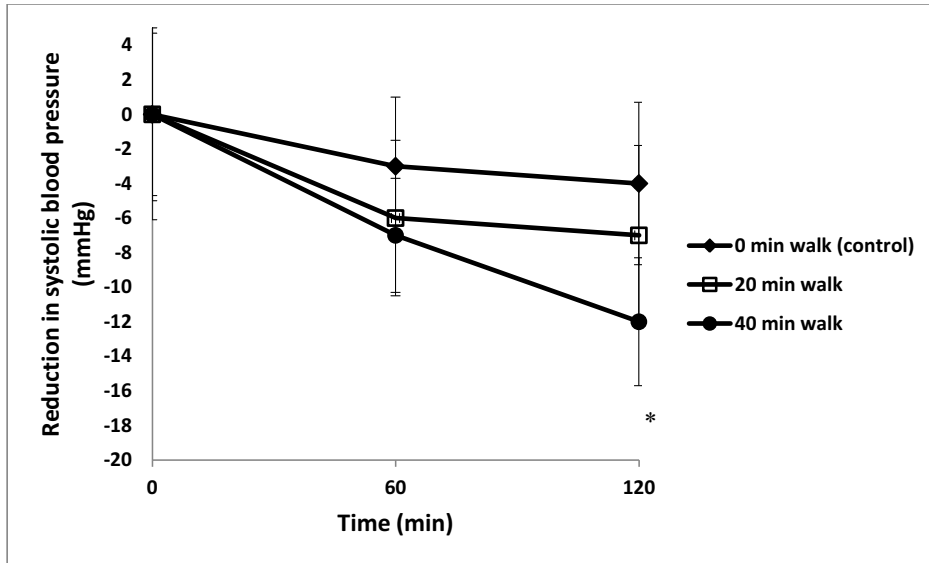
**Figure 3:** Glycemic response (Incremental area under the blood glucose curve, IAUC) to cornflake ingestion without postmeal walking (x-axis) as related to the IAUC reduction caused by 40 min slow postmeal walking (y-axis).

**Correlation coefficient (Kendall's Tau),  $r = -0.719$ ;  $p = 0.004$  ( $n = 10$ ).**

*Will slow post meal walking reduce the blood pressure?*

A significant reduction in systolic blood pressure (SBP) was observed at 2h in the 40 min walking experiment as compared with the 2h SBP reduction on the control day ( $p < 0.05$ ). The reduction in SBP at 2h in the 20 min experiment was not significantly different from the response on the control day (Figure 4). No changes in diastolic blood pressure were observed due to light post meal walking.





**Figure 4: Systolic blood pressure as influenced by postprandial very light physical activity (slow walking).** On three separate days the blood pressure was determined before (time=0) ingestion of cornflakes and milk, providing 50 g carbohydrates, and then again after 1h and 2h. One of the test days included a 20 min walk (from 15 to 35 min) (open squares, n=11), another test day the subjects walked 40 min (from 15 to 55 min) (closed circles, n=10) after the meal, whereas the y the participants sat resting for the entire 2h period the control day (closed squares, n=11). **Mean values  $\pm$  SEM.** Note broken y-axis. \*  $p < 0.05$  vs. corresponding value on the resting day.

## DISCUSSION

The present results show that even very slow walking can blunt the post meal rise in blood glucose, and reduce systolic blood pressure in a group of diabetes prone subjects. All of the Pakistani immigrant women participating in the present study had high postprandial blood glucose responses, and 3 were diagnosed as diabetics. Diabetes prone subjects are generally encouraged to increase the level of physical activity to achieve good blood glucose control.

However, the only physical activity regularly performed by the present study group is slow walking. Surprisingly, also such low intensity physical activity seems to strongly attenuate the blood glucose elevation, when performed immediately after the meal. It would appear, accordingly, that slow walking after carbohydrate intake could be an efficient approach to improve the glycemic control in the current diabetes prone group.

We believe that the repeated measures ANOVA does actually model changes over time in blood glucose level, as it is modeling changes from a chosen reference time point to each subsequent measurement. However, it can be argued that other models and methods, among them generalized estimating equations, are more flexible with regard to their ability to model time developments and covariance structures. Due to the rather small sample size in this study, such models will, however, be difficult to fit.

Possible contributors to the disparity in prevalence of T2D seen in female Pakistani immigrants may be related to genetic and cultural factors. Thus, Dickinson et al. (2002) found that the postprandial hyperglycemia and insulin sensitivity varied among different ethnic groups, and that lean, young South East Asians had the highest postprandial glycemia and the lowest insulin sensitivity in response to a realistic carbohydrate meal (20). However, female Pakistani immigrants living in Norway show a higher prevalence of T2D than female Pakistani in their native country indicating an additional cultural component (21). Kandula et al. (22) found a higher prevalence of T2D among acculturated immigrants and concluded that acculturation is a factor that should be considered when predictors of T2D in immigrants are examined. On the other hand, it seems that Pakistani immigrants in Norway adopt the local habits concerning use of carbohydrate rich food items (23). However, to our knowledge it has

not been established to what extent the elevated T2D prevalence found among immigrants in Norway have cultural or genetic explanations.

Walking seems to be a beneficial form of physical activity for diabetics (24). The present results strongly suggest that low intensity post meal walking may represent a "low barrier" lifestyle advice that could have an appreciable preventive potential, if regularly performed. Further studies are however needed to substantiate this hypothesis, and to clarify the optimal work duration and intensity required to blunt the post meal glucose elevation.

In studies involving repeated carbohydrate intakes great care should be taken to avoid carry over effects on the postprandial blood glucose curves. It is well known that there is an improved carbohydrate tolerance after repeated glucose intakes, which in part seems to be caused by increased insulin response to repeated carbohydrate intakes (25). However, the Staub-Traugott and other carry over effects are unlikely to take place under the conditions of the present work, in which there was as long as 7 days between the trials. On the other hand, variations in diet and physical activity during the last couple of days before each experiment could possibly influence the results. In an attempt to control for this, the participants were asked to behave as similarly as possible on the day before the experiments, and to fast for 12 hours before the experiments started each morning. Since the participants complied with this requirement, we do not consider that alterations in lifestyle during the trial period had a major influence on the outcome. Nevertheless, anticipating that there in theory could be variation in diet and physical activity on different days of the week, for each subject we chose to do all the experiments on the same day of the week.

This study did not aim at exploring mechanisms involved in the effects of walking on blood glucose. Among potential explanations of the glucose lowering effect of physical activity is an effect to stimulate GLUT4 translocations to the cell membrane, thereby facilitating glucose transport into the cell. It is well established that there are two distinct intracellular pools of glucose transporters in skeletal muscle, one responding to exercise and another responding to insulin (26). It would seem, therefore, that insulin resistant subjects could have special benefit of doing physical activity to attenuate the glucose elevations after carbohydrate rich meals.

Blood glucose levels are influenced by psychological stress. The prevalence of T2D is low in individuals with good coping skills (27). Both acute and chronic stress affects the cardiovascular system (28). People having elevated risk of getting diabetes often experience a general activation which in turns may lead to elevated blood glucose. Being familiar with what influences their own blood glucose levels may be an important “stress reducer”.

In this study we found that the glucose lowering effect of walking was most pronounced for subjects with large IUAC on the control day. The results are in keeping with the results obtained in previous studies comparing the influence of low-glycemic vs. high-glycemic foods (29), and the effect of exercise (12). We emphasize, however, that in this type of experiments it is difficult to control for the regression to the mean effect (30). In fact, it is hard to appreciate the relative contribution of the latter effect and a true biological effect.

In this study we found that an acute exercise session promoted the lowering of systolic blood pressure during the post exercise period. In line with Lima et al. (31) we found that even slow walking lowered systolic blood pressure. Furthermore, in line with Mach et al. (32) only the longest duration of light post meal physical activity gave a reduction in blood pressure.

Among possible mechanisms involved in the regulation of short term arterial blood pressure are activity of autonomic nerves, concentration of hormones (e.g. epinephrine, angiotensin II, vasopressin), or other vasoregulatory components such as nitrogen oxide, but the present study does not clarify any mechanisms of action.

As observed in the present study, repeated measurements of blood glucose during a test period which also involved a session of physical activity seemed fairly understandable for the participants. Thus, participation in this study seemed suitable to enable the subjects to translate knowledge about blood glucose regulation into a practical lifestyle change that could reduce the risk of diabetes. Studies are currently in progress to assess this hypothesis.

The sample size of the study was small, making the study to appear exploratory. In particular, the ability to generalize the findings is reduced; however, the cross over design of the study would reduce the measurement variability. Furthermore, several previous similar studies with a comparable small number of participants found highly significant effects of post meal light physical activity on the blood glucose responses (10-12). Also in glycaemic index testing, using a crossover design, only ten subjects are regularly used (18;33). Nevertheless, the low number of participants is a limitation concerning external validity.

Even though the sample size was sufficient to detect significant differences in blood glucose excursions after light post meal physical activity vs resting, it could be questioned whether observations based upon 10 subjects are valid for the general population. However, the finding that light post meal physical activity blunts the blood glucose increase has been repeatedly shown in other population groups: in healthy ethnic Norwegians of both sexes, in young and middle-aged subjects, and in trained and sedentary ones (10-12). It thus appears

that the blood glucose modifying influence of light post meal physical activity is a general physiological response. The specific question in our article was therefore to investigate whether slow post meal walking would have a blood glucose blunting effect **also** in a group of diabetes prone immigrant women, since previous studies had demonstrated this effect in other groups. However, the findings should be confirmed in larger randomized controlled trials among diabetes prone subjects to obtain an appropriate estimate of the blunting effect of light post meal physical activity in the current and other diabetes prone immigrant population groups.

## **CONCLUSIONS**

Very slow post meal walking after ingesting a high glycemic meal can appreciably reduce the rise in blood glucose and also reduce the systolic blood pressure, as observed in female Pakistani immigrants living in Oslo. These exploratory observations thus seem to provide a basis for a practical lifestyle advice for prevention of T2D.

## **NEW CONTRIBUTIONS TO THE LITERATURE**

Even very low intensity post meal walking can blunt the rise in blood glucose and reduce the systolic blood pressure in diabetes prone Pakistani immigrant women, and should be considered as a lifestyle advice for prevention of type 2 diabetes in this group.

## **ACKNOWLEDGEMENTS**

The technical assistance of Eva Kristensen and Monica Morris is gratefully acknowledged.

**Table I. Baseline characteristics of the participants.**

	Mean	SD
Age (years)	44	9.3
BMI (kg/m <sup>2</sup> )	30.9	6.7
Waist circumference (cm)	101	14.6
Blood pressure (systolic/diastolic)(mmHg)*	115/79	17/10
HbA1c (%)	5.5	0.4
Fasting blood glucose (mmol/L)*	5.5	0.6
Fasting blood glucose (mmol/L)**	5.5	0.5
2-h blood glucose value (mmol/L)** (OGTT)	9.4	2.0

\* Mean value of 9 measurements (3 measurements each of the 3 experimental days).

\*\* Mean value of 3 measurements performed during the standardized OGTT.



**Table II: Postprandial blood glucose peak value (PV) and time to reach PV from zero time (TTP) as influenced by the duration of very light post meal walking.**

	Control		20 min walk		40 min walk	
	Mean	SD	Mean	SD	Mean	SD
PV (mM/L)	9.8	1.4	9.0	1.2	8.2 <sup>a, b</sup>	0.9
TTP (Min)	43.6	12.5	62.7 <sup>c</sup>	11.3	69.0 <sup>a</sup>	19.0

Student-t test paired samples.

a)  $p = 0.001$  vs. control.

b)  $p = 0.016$  vs. 20 min walk.

c)  $p = 0.002$  vs. control.

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